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Home dialysis for the treatment of end stage chronic kidney disease

Annabel Boyer

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Normandie Université

THÈSE

Pour obtenir le diplôme de doctorat

Spécialité RECHERCHE CLINIQUE, INNOVATION TECHNOLOGIQUE, SANTE PUBLIQUE

Préparée au sein de l'Université de Caen Normandie

Home dialysis for the treatment of end stage chronic kidney disease

**Présentée et soutenue par
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**Thèse soutenue le 09/12/2021
devant le jury composé de**

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Santé, Environnement



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Table of contents

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Acknowledgments	1
List of tables	5
List of figures	6
Abbreviations	7
I. General introduction	9
1. End stage kidney disease	9
A. Definition	9
B. Epidemiology	10
C. Preparing for dialysis	12
D. Kidney replacement therapies	13
E. Conservative care	13
F. End stage kidney disease in the elderly	14
2. The place of peritoneal dialysis in the integrated treatment of end stage kidney failure	15
A. The concept of integrated care	15
B. Peritoneal dialysis and integrated care	17
C. Assisted peritoneal dialysis	17
3. Investigating the reasons of PD under-utilization	20
A. Epidemiology	20
B. Reasons of PD under-utilization	22
II. Peculiarity of the methods	24
1. Time varying covariate	24
2. Fractional polynomials	27
3. Temporal trend analysis	28
4. Competing risk analysis	30

5.	Multiple imputation	34
III.	Impact of the implementation of an assisted peritoneal dialysis program on peritoneal dialysis initiation	36
1.	Introduction.....	36
2.	Materials and methods	37
3.	Results	39
4.	Discussion	44
5.	Article	45
IV.	Trends in assisted peritoneal dialysis usage over the last decade.....	8
1.	Introduction.....	8
2.	Materials and methods	8
3.	Results	10
4.	Discussion	11
5.	Article	12
V.	Trends in peritoneal dialysis technique survival, death and transfer to haemodialysis	10
1.	Introduction.....	10
2.	Materials and methods	11
3.	Results	13
4.	Discussion	13
5.	Article	15
VI.	Time spent on HD before transitioning to PD impacts PD outcomes	26
1.	Introduction.....	26
2.	Materials and methods	26
3.	Results	28
4.	Discussion	28
5.	Article (submitted)	30
VII.	Discussion	53
1.	Main results.....	53

2. Perspectives.....	55
A. PD technique failure.....	55
B. Trends in registration rates on the transplant waiting list of incident dialysed patients aged over 70 years over the past decade	58
C. Home dialysis implementation, an international comparison.....	60
D. Transfer from HD to PD	62
E. Investing strategies towards a free choice for all	62
3. Conclusion	63
Bibliography.....	64
Communications in the course of the thesis.....	78
Collaborations outside of the course of the thesis linked with the thematic area.....	79
Other publications outside of the course of the thesis.....	80
Résumé en français	81

List of tables

Table 1. GFR categories in chronic kidney disease

Table 2. Features of the elderly patient affecting management of ESKD

Table 3. Assisted PD programs according to the country

Table 4. Description of the age according to KRT and PD characteristics

Table 5. Association between the availability of assisted PD and the hazard rate of PD initiation, adjusting for patient characteristics.

List of figures

Figure 1. REIN annual report, synthesis

Figure 2. Suggested concept of integrated care

Figure 3. Average monthly cost per treatment modality for a stable prevalent patient

Figure 4. United Kingdom Renal Registry 19th annual report, modality changes in prevalent KRT patients from 2000-2015

Figure 5. Distribution of home dialysis by area across the French territory

Figure 6. Long-term effect of baseline risk factor on mortality

Figure 7. Effect of time-varying risk in mortality

Figure 8. Schematic of a cox regression with robust variance

Figure 9. Cause-specific hazard ratio illustration

Figure 10. Sub-distribution hazard ratio illustration

Figure 11. The three stages of multiple imputation

Figure 12. Methodology of the study

Figure 13. Effect of assisted PD service on the hazard rate of PD initiation over time

Figure 14. Effect of time on the rate of PD initiation

Figure 15. Prevalence ratio of assisted PD initiation over time

Figure 16. Description of the events of interest

Abbreviations

95% CI: 95% confidence interval

ANZDATA: Australia and New-Zealand Dialysis and Transplant Registry

APD: Automatic peritoneal dialysis

CAPD: Continuous ambulatory peritoneal dialysis

CKD: Chronic kidney disease

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

CORR: Canadian Organ Replacement Registry

cs-HR: Cause-specific hazard ratios

ESKD: End stage kidney disease

FP: Fractional polynomials

GFR: Glomerular filtration rate

eGFRs: Estimated GFRs

HD: Haemodialysis

HHD: Home haemodialysis

HAS: Haute Autorité de Santé

KDIGO: Kidney Disease Improving Global Outcomes

KRT: Kidney replacement therapy

MDRD: Modification of Diet in Renal Disease

MI: multiple imputation

MICE: multiple imputation by chained equation

PD: Peritoneal dialysis

Pmi: Per million inhabitants

PR: Prevalence ratios

RDPLF: French Language Peritoneal Dialysis Registry

REIN: Réseau Epidémiologique en Néphrologie

sd-HR: Sub-distribution HR

UK: United Kingdom

UKRR: United Kingdom Renal Registry

USA: United State of America

USRDS: United States Renal Data System

I. General introduction

1. End stage kidney disease

A. Definition

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function present for at least 3 months, with implication for health. Abnormal urinalysis results identifying proteinuria or haematuria and abnormal kidney structure or histologic features, with or without a decreased glomerular filtration rate (GFR) are the defining manifestations. CKD is recognized as a major public health issue because of its high prevalence and related complications (1). It is classified based on cause, GFR category and albuminuria category, with five assigned GFR categories (stage I to stage V) (table 1).

GFR can be measured provided that the concentration of a substance that is freely filtered at the glomerulus and neither reabsorbed nor secreted in the renal tubule is measured in the plasma and in a timed urine collection (creatinine, inulin...), which can be cumbersome. As an alternative to direct measurement, estimated GFRs (eGFRs) can be calculated using the values of plasma creatinine accounting for other factors such as age, sex, weight and height which are known to impact creatinine serum concentration. The most commonly used methods include the MDRD (Modification of Diet in Renal Disease) and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration).

End stage kidney disease (ESKD), or kidney failure, is defined according to the Kidney Disease Improving Global Outcomes (KDIGO) (1) and the French "Haute Autorité de Santé" (2) by a GFR persistently below $15\text{mL}/\text{min}/1,73\text{m}^2$ or the need of a kidney replacement therapy (KRT). Information on untreated kidney failure, $\text{GFR} < 15\text{mL}/\text{min}/1,73\text{m}^2$ not treated by KRT, remains unknown as it is not captured by national registries. Because dialysis is the

predominant mode of KRT, the epidemiology of ESKD largely reflects the epidemiology of dialysis.

Table 1. GFR categories in chronic kidney disease

Stage	Description	Estimated GFR <i>mL/min/1.73m²</i>
I	Kidney damage with normal or increased GFR	>90
II	Kidney damage with small decrease in GFR	60-89
IIIA	Kidney damage with small to moderate decrease in GFR	45-59
IIIB	Kidney damage with moderate to large decrease in GFR	30-44
IV	Kidney damage with large decrease in GFR	15-29
V	Kidney failure	<15

GFR: glomerular filtration rate

B. Epidemiology

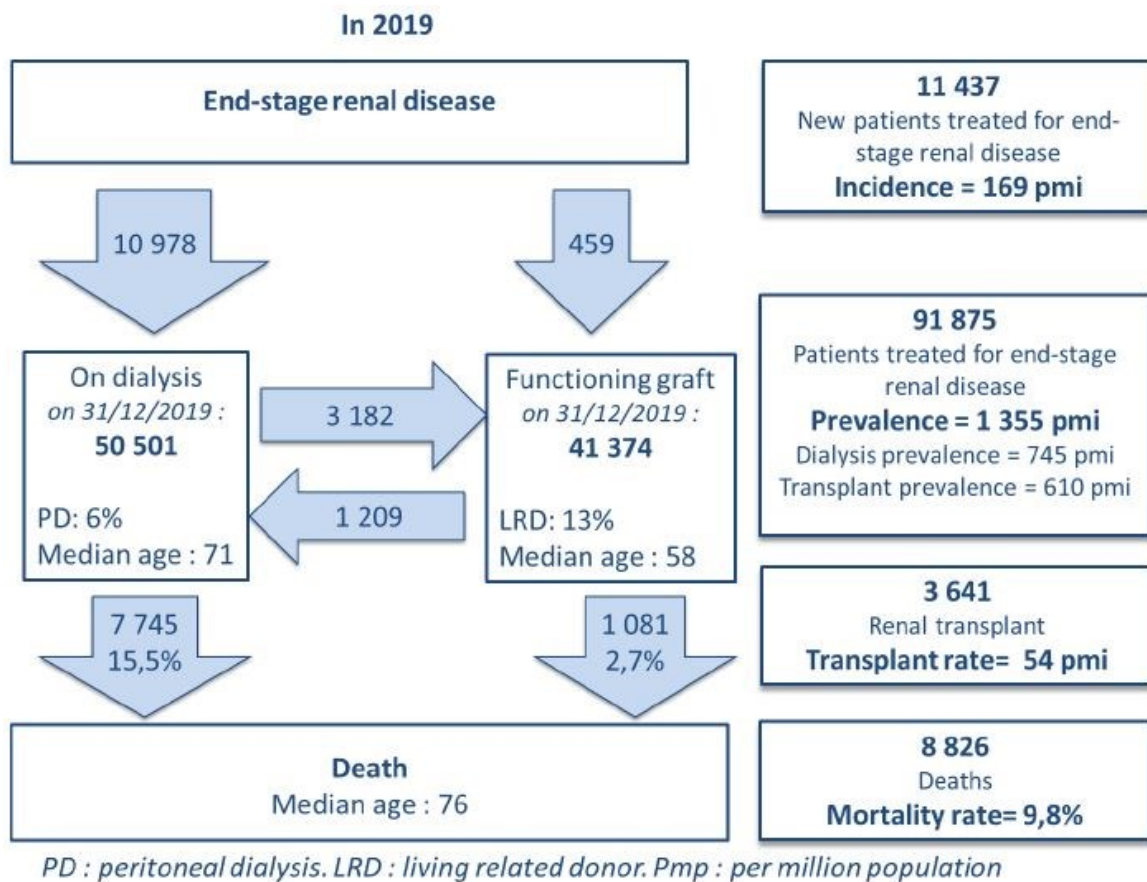
The incidence and prevalence of ESKD defined by a GFR below 15mL/min/m² remains unknown. If the number of patients treated by KRT is well established via national registries, the number of patients with a stage V CKD but not treated by KRT is not captured in the registries.

In France, the Réseau Épidémiologique en Néphrologie (REIN) registry records information on all patients with ESKD who start KRT (dialysis or preemptive transplantation). The registry was launched in 2002 and covers the whole French territory since 2012. It includes data on the patient and center's identification, primary renal disease, clinical characteristics,

comorbidities and modality of ESKD management. Data are collected when the patients start KRT. Patients are then followed annually, and specific events (change of KRT, death, transplantation...) are recorded on occurrence (3,4). A registry specific to PD is also available in France, the French Language Peritoneal Dialysis Registry (RDPLF). The RDPLF was created in 1988 in order to promote research and improve the quality of care given to ESKD patients treated with PD. The main module registers data on patient and center's characteristics, comorbidities, PD management and complications, transplantation. Other optional modules collect data on nursing and teaching methods, catheters, anemia, cardiac failure, nutrition and adequacy of dialysis.

According to the REIN, in France in 2019, 11 437 new patients were treated by dialysis and 459 received a kidney transplant as first treatment of ESKD, with an overall incidence of treated ESKD of 169 per million inhabitants (pmi). On December 31, 2019; 91 875 patients were receiving a KRT for ESKD, 55% on dialysis and 45% living with a functional kidney transplant (figure 1). The overall crude prevalence was 1 355 pmi (4).

Figure 1. REIN annual report 2018, synthesis



C. Preparing for dialysis

As the kidney function declines, below 20mL/min/1.73m², the focus of care changes from preservation of remaining kidney function to KRT preparation. Effective preparation for KRT requires a multidisciplinary approach and education program (medical, nursing, dietetics, psychology and social work) (5–7). The initiation of dialysis can be emotionally challenging for patients and families, presenting patients with choice of modality may ease the burden of stress and anxiety. Patients require adequate counselling to assist them in the choice of dialysis modality, best adapted to their conditions, and in coping with the psychosocial effects of starting KRT (8,9). Patients involved in modality selection tend to be more satisfied with their treatment (10).

If patients have been referred in a timely manner, preparation for KRT should already be complete (2,11), however ongoing psychosocial support is often necessary as the patient comes to terms with the imminent need to start therapy.

D. Kidney replacement therapies

Kidney replacement therapies includes dialysis and kidney transplant. For patients requiring KRT, transplantation is associated with better outcomes (12,13) and quality of life (14–16), and lower costs (17), but is not possible for all patients.

Multiple dialysis modalities are available, some can be performed in dialysis facilities and other at home. Hospital dialysis is represented by in-centre haemodialysis (HD) whereas home dialysis includes home HD (HHD) and peritoneal dialysis (PD), which can be divided in two modalities: automatic peritoneal dialysis (APD) or continuous ambulatory peritoneal dialysis (CAPD). Studies have failed to indicate a consistent survival advantage for either modality (18,19). Ideally, all patients presenting ESKD would be given “modality-neutral” counselling and allowed to choose freely their preferred dialysis modality (9,10).

E. Conservative care

Conservative care, or active medical management without dialysis, is defined by active nephrology care without dialysis initiation or kidney transplant. This approach is widely recognized and delivered. It includes interventions to delay progression of kidney disease and minimize ESKD complications, shared decision making, active symptom management, psychologic and social support (20,21).

F. End stage kidney disease in the elderly

The incidence of ESKD is increasing most rapidly in people aged 65 years and older (4,22). This population is at increased risk of developing age-relating issues such as frailty, falls, poor nutrition and cognitive impairment (23–26). All of these factors have an impact on the management of ESKD (table 2).

Even though age itself is no longer a contraindication for transplantation, the majority of these patients will have too many comorbidities to be eligible (4,27). ESKD elderly patients are often left with the options of dialysis and conservative care. Yet, it has been showed that a high proportion of elderly patients observe a decline in functional status in the first six months after initiating dialysis (28). When choosing dialysis, the default treatment option for these patients is often in-centre HD, despite how this modality will impact their quality of life. Transport to and from the dialysis unit, rapid changes in hemodynamic and fluid status and vascular access complications increase the patient's burden (29–32). Peritoneal dialysis, being a home-based treatment, has the advantage of preserving the autonomy.

In addition, it must be reminded that dialysis may not extend survival for patients with multiples comorbidities, in which case conservative care should be considered. In this elderly population, the approach should focus on the overall prognosis, the quality of life and how the patients cope with their disabilities and end-of-life goals (33).

Table 2. Features of the elderly patient affecting management of ESKD

Physical factors	Psychosocial factors
Impaired physical function	Social isolation
Cognitive dysfunction	Bereavement
Impaired nutrition	Need for social support
Visual problems	Financial issues
Deafness	

2. The place of peritoneal dialysis in the integrated treatment of end stage kidney failure

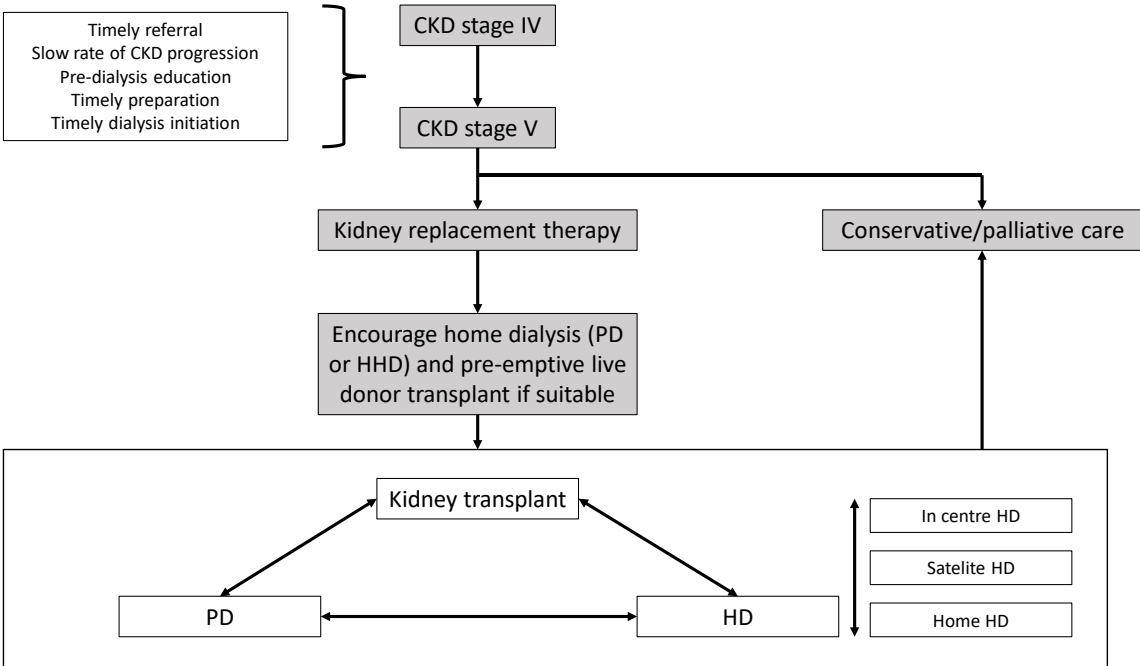
A. The concept of integrated care

Over the past decades, studies have failed to identify the optimal KRT, and we have come to understand that most patients will use different therapy modalities at different time points of their disease. Indeed, a single therapy might not be adequate across the pathway of a patient with ESKD, and many patients will require a transition in modality to adapt the treatment to their clinical needs. A patient might change its treatment modality because of a previous modality failure (kidney graft failure or PD failure notably), of a change of lifestyle and reconsideration of his initial modality choice, of a medical situation that requires a change in dialysis modality or more frequent treatment prescriptions, or of a kidney transplantation (8,34). According to their specific medical situation, patients can transition between different KRT modalities, including kidney transplantation, PD, in centre HD, satellite HD and HHD, or decide to opt for conservative care (34).

Thus, KRT modalities should be considered as complementary rather than competitive, each therapy should be freely available and used as appropriate according to the clinical

situation and patients' choice. In this case, comprehensive pre-dialysis education explaining the available options of all KRT modalities is essential (1,5–8,10,35). The patients' treatment pathway is now considered as integrated care and includes a succession of different KRT modalities rather than a single one, as suggested in Figure 2 (35–44).

Figure 2. Suggested concept of integrated care



B. Peritoneal dialysis and integrated care

The concept of integrated care has been interpreted differently throughout the world according to the countries' background and healthcare system. Indeed, in some part of the world it has been implemented as a medical policy consisting in the initiation of PD as first KRT followed by a timely transition to in centre HD when necessary (45–49). This PD-first strategy has proven to be efficient in terms of survival, preservation of kidney residual function, protection of potential vascular access and economic considerations (44,45,48–53).

Indeed, PD has been associated with a better quality of life (54–56), better outcomes in the first 2-3 years and preservation of residual kidney function (50,52,57–59), and lower costs than in-centre HD (51,60,61). It enables the patient to preserve a high degree of autonomy, to travel and have an active life. In addition, compared to in-centre HD, PD offers several advantages such as the avoidance of transport to and from the dialysis unit, avoidance of difficulties in creating vascular access, and hemodynamic instability during the HD session (29–32).

Despite these advantages, some barriers to PD remain, such as older age, frailty, comorbidities, physical disabilities and social problems (29,62–65). Indeed, very few elderly and frail patients are able to perform their dialysis treatment on their own. In some instances, family members might help. However, when this is not possible and in the absence of assisted PD programs, most of these patients are placed on HD when some might opt for conservative care (33).

C. Assisted peritoneal dialysis

The conditions that act as a barrier to self-care PD can be overcome by assisted PD, where a trained staff or family member provides daily dialysis assistance in the patient's home

or in nursing home (64,66). Assistance can thus improve accessibility of home dialysis and survival in elderly or frail patient (29,66,67), whose quality of life may benefit most from home care dialysis (55).

Home assistance programs have been implemented in several countries in recent decades. Depending on the country and reimbursement system, the assistance can be provided by a healthcare technician, a community nurse, a trained family member or partner (table 3) (31,68). The type of assistance, either by a trained health-care or a family member, is not always provided in national registries, making national and international comparisons difficult.

Table 3. Assisted PD programs according to the country

Country	Type of PD	Caregiver	Number of visits per day
France	APD and CAPD	Private nurse	2 to 4
Denmark	APD	Community nurse	2
Italy	APD and CAPD	Health care assistant	2
United Kingdom	APD	Health care assistant	1
Canada (On, BC)	APD and CAPD	Community nurse	2
China	CAPD	Health care assistant	Unknown
Taiwan	APD and CAPD	Foreign domestic worker	Unknown

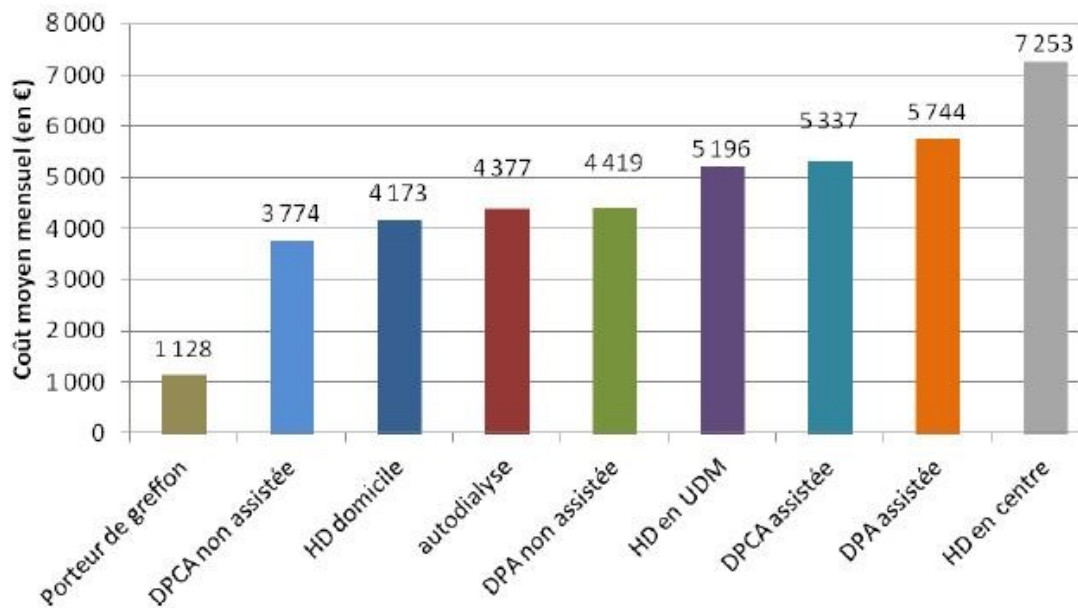
On: Ontario, BC: British Columbia, PD: peritoneal dialysis; APD: automated peritoneal dialysis; CAPD: continuous ambulatory peritoneal dialysis

With the first programs being implemented in the 1980s, France has one of the longest experiences of assisted PD (69,70). Private nurses are paid for the dialysis procedure at the

patient's home or nursing home: performing PD exchanges up to four times a day for CAPD, setting up the cyclor and doing the connection for APD. Most of the time, nurses are trained for PD in a public nephrology department.

Nurse-assisted PD is fully covered by the French health care insurance (71). In addition to the many advantages' PD provides in the elderly population, assisted PD remains cheaper than in-centre HD and medically supervised HD units, even after the additional costs for nurse assistance. However, because of the added costs of assistance, the cost for a stable patient in assisted PD is higher than for a patient in self-care HD unit (figure 3) (2,72). It has been demonstrated that in young patients with diabetes and middle-aged patients without it, developing HD in self-care units would save more money than expanding non-assisted PD (73). Thus, the choice of assisted PD shouldn't be based on economic grounds but rather for the quality of life and patients' preferences.

Figure 3. Average monthly cost per treatment modality for a stable prevalent patient



Porteur de greffon: transplanted patient ; DPCA non assistée : non assisted CAPD ; HD domicile : home HD ; autodialyse : self-care HD unit ; DPA non assistée : non assisted APD ; HD en UDM : medically supervised HD units; DPCA assistée: assisted CAPD; DPA assistée: assisted APD; HD en centre: in centre HD

Assisted PD allows patients to choose their PD modality (APD or CAPD) and the type of assistance (nurse or a family-assisted PD). According to the RDPLF, over 50% of incident patients treated by PD from 1995 to 2006 were considered unable to perform self-care PD and needed assistance. In the elderly population, over 80% needed assistance (74). In a study based on the REIN registry, PD was chosen significantly more often than planned HD by older patients (aged over 85 years) compared to younger patients (75).

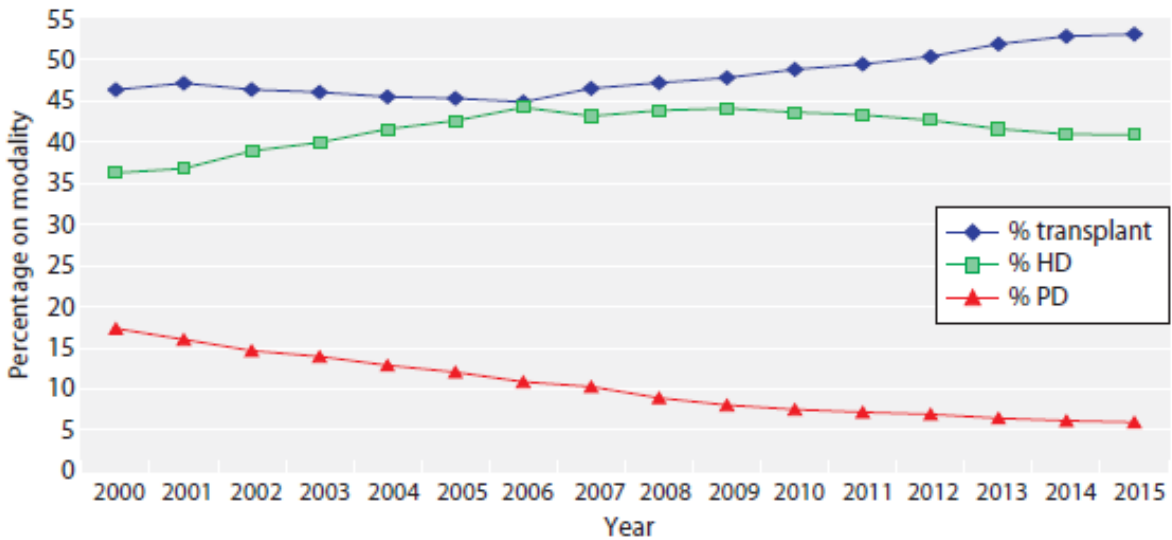
3. Investigating the reasons of PD under-utilization

A. Epidemiology

PD usage has been declining in the past decades, while the total number of dialysis patients has increased (4,76,77). Between 1997 and 2008, the proportion of dialysis patients treated with PD significantly declined by 5.3% in developed countries (76). In France, the PD

prevalence in 2018 was of 44 per million population, compared to 42 per million population in 2012, while the total number of patients on KRT increased by 20% (4,78). In the United Kingdom (UK), the PD prevalence in 2015 was of 55 per million population, a reduction of 6.2% compared with 2005 (figure 4) (77,79).

Figure 4. United Kingdom Renal Registry 19th annual report, modality changes in prevalent KRT patients from 2000-2015



In Europe, only 13-25% of patients aged 65-74 years, and 9-13% of those aged over 75 years, start on PD, compared with 20-41% of patients aged 45-64 years (80). France stands out from the other European countries, with a higher proportion of patients aged over 75 years on PD compared to younger patients (4).

At a national level, a wide disparity in PD usage is observed across the French territory, as described in figure 5, with differences in structural organization between PD centres (4). These differences impact PD outcomes. Indeed, centre effect has been associated with early PD failure, centre experience being associated with a lower risk of transfer to HD (81).

Figure 5. Distribution of home dialysis by area across the French territory

REIN registry 2018

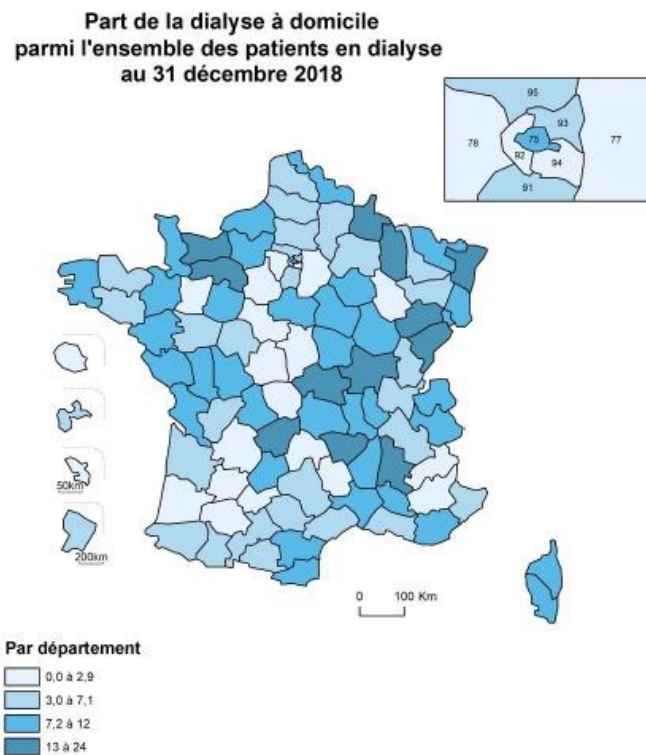


Figure 4-2. Part de la dialyse à domicile, par département
Distribution of home dialysis, by area

B. Reasons of PD under-utilization

Several reasons could explain this PD under-utilization. First, PD uptake remains insufficient, as indicated by the decreasing incidence over time. It is unclear whether this decline is linked to an aging population, which may be associated with limited use of home therapy unless an assistance is provided. It would be anticipated that provision of an assisted PD service, by removing some of the barriers to home dialysis, should increase the number of patients eligible for PD and thus increase PD initiation, however, this has never been demonstrated before. In the first part of the thesis, we have investigated the impact of the implementation of an assisted PD service on PD initiation. With the present study, we have reported how the introduction of an assisted PD service positively influenced the uptake of

PD and counterbalanced the decline in PD rates over time, particularly providing PD as an option for older and frailer patients.

Following this finding, we questioned ourselves on strategic incentives which could promote assisted PD programs. Indeed, economic incentives altering remuneration for assisted PD in nursing homes have been recently introduced in France in order to further encourage PD usage for older patients in nursing homes, but their impact remains unknown to date. Therefore, in the second part of the thesis, we aimed at describing assisted PD utilization over the past decade in France. With the CKD population growing older and frailer, an increase in assisted PD utilization over time would be anticipated. However, our results showed a different pattern: due to a linear decline in family assistance, assisted PD currently relies mainly on nurse assistance. An uptake in nurse-assisted PD was observed since 2013, probably reflecting the effect of an economic incentive adopted in late 2011 to increase PD utilization for end-stage renal disease patients in nursing homes.

Another limitation to PD expansion relates to technique survival, which remains a major concern for ESKD patients and their nephrologists (82,83). Indeed, transfer to HD could partially explain the low PD prevalence. Even though significant improvements have been observed in rates of peritonitis, a major cause of technique failure (84), only few studies in the literature describe longitudinal trends in PD technique survival (59,85–87). Therefore, we have pursued our research, and studied the evolution of PD technique survival (death or transfer to HD), transfer to HD and the individual causes of transfer to HD, and patient survival over the past decade in France. We have shown that in France, rates of PD cessation due to either death or transfer to HD, death, and transfer to HD have decreased in recent decades. The decline in transfer to HD rates is mainly due to a significant decline in infection-related transfers, and particularly in self-PD patients.

Finally, in the context of integrated care, it is now acknowledged that the patients' treatment pathway includes a succession of different dialysis modalities rather than a single one. Data regarding the outcomes of patients transferring from HD to PD are still scarce. One could expect that the time spent on HD before transitioning to PD would impact PD outcomes, however this has never been described in the literature. In the last part of the thesis, we conducted a registry-based study aiming to report the effect of transitioning from HD on PD technique survival, death, and retransfer to HD, accounting for the effect of time spent on HD before transitioning to PD. We have demonstrated that the transition from HD to PD is a rare event, often understudied, mostly happening early in the course of KRT. Time spent on HD before transfer to PD impacts patient survival but does not impact retransfer to HD, and importantly the effect of the time spent on HD on the risk of PD cessation seems to increase gradually over time.

In this work, we combined data of patients on PD from France and the UK, using statistical models adapted to address some of the gaps in the current knowledge in PD under-utilization.

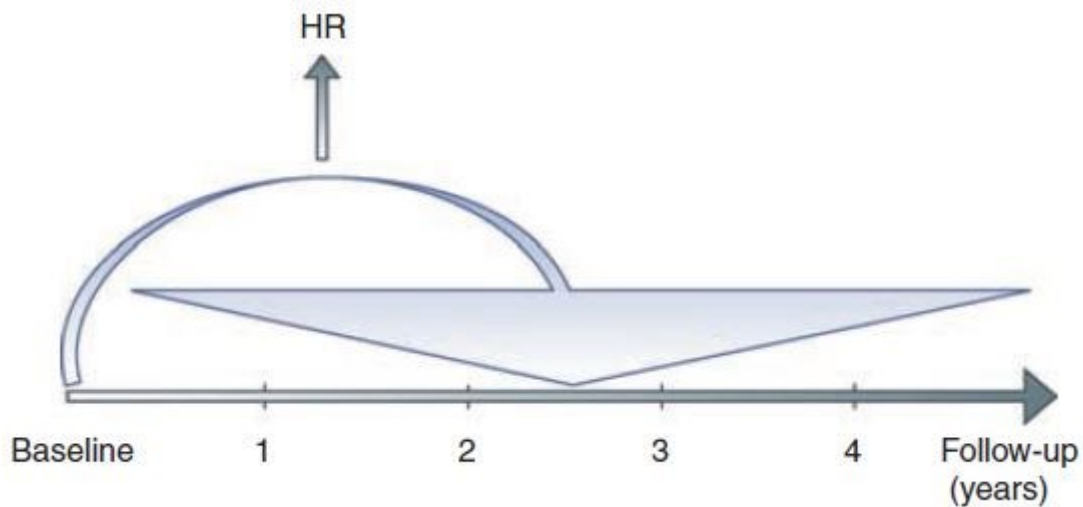
II. Peculiarity of the methods

1. Time varying covariate

When explanatory variables are incorporated in a model for survival data, the values taken by such variables are usually those recorded at the time origin of the study. In traditional Cox regression analysis, a risk factor measured at baseline is related to an event thereafter (figure 6); which doesn't always reflect the reality. Indeed, the exposition to a risk factor may change over the study period (88).

Figure 6. Long-term effect of baseline risk factor on mortality

Friedo W. Dekker, *Kidney International*, 2008



A time-varying covariate, or time-varying risk factor, is a risk factor whose value changes over time. Two types of variables that change over time can be considered: *internal* and *external* variables. Internal variables relate to a particular patient in the study, and can thus only be measured while the patient is alive. Such data emerges when repeated measures of a variable are made on the same patient over time, such as blood pressure or blood test for example. Whereas external variables do not necessarily require the survival of the patient and is thus not directly linked to the failure mechanism, such as the dose of a treatment that will vary in a fixed way over the course of the study.

Cox regression is used to analyse time-to-event data. Consider the general hazard model where $h_0(t)$ is the baseline hazard function and β' a vector of regression coefficients. In the usual form of Cox regression, X is a vector of time-fixed covariates:

$$H(t|X)=\exp(\beta' * X)*h_0(t)$$

Then, the hazard of an event at time t in a study in which the explanatory variable is time-dependent can be written as followed:

$$H(t|Z(t)) = \exp(\beta'x + \gamma'Xg(t)) * h_0(t)$$

where $h_0(t)$ is the baseline hazard function, β' and γ' the regression coefficient of time-fixed and time varying covariates, and X the covariate allowing incorporation of a time interaction function $Xg(t)$ (the value of the variable at time t). $Z(t)$ represents the several covariates as following: $Z(t) = [x_1, x_2, \dots, x_p, X_{1g}(t), X_{2g}(t), \dots, X_{qg}(t)]$. Then the hazard ratio (HR) is:

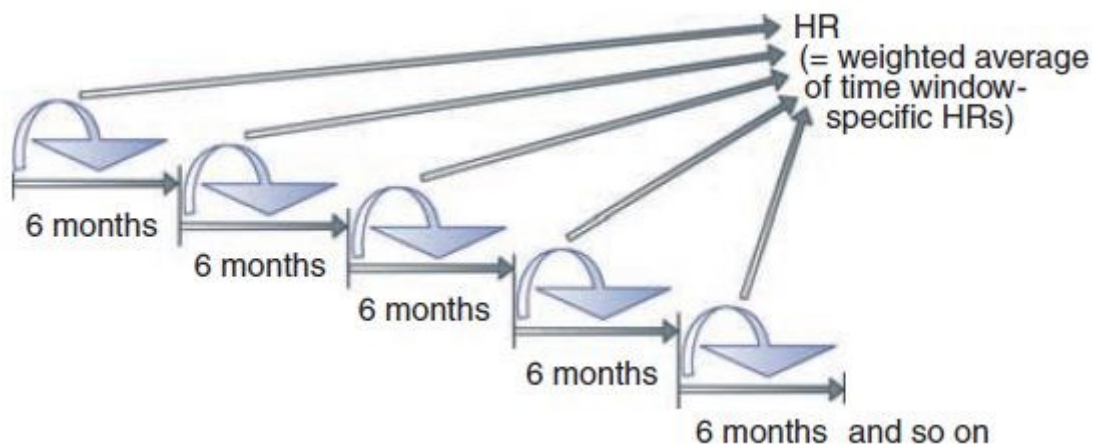
$$HR = [H(t|Z(t)) / H(t|Z(t)^*)] = \exp(\beta'x^* + \gamma'Xg(t)^*)$$

which is a non-constant hazard-rate. In this model the baseline hazard function $h_0(t)$ is interpreted as the hazard function for an individual for whom all the variables are zero at the time origin, and remains the same value through time. Since the value of the variable $X(t)$ depend on the time t , the relative hazard $H(t) / h_0(t)$ is also time-dependent.

In Cox regression with time-dependent covariate, one defines a time-varying factor that refers to several measurements of that risk factor during follow-up, and includes that variable in the Cox regression model (figure 7). In this kind of analysis, the follow-up time for each patient is divided into different time windows. In the first hand, for each time window, a separate Cox analysis is carried out using the specific value of the time dependent covariate at the beginning of that specific time window. In the second hand, a weighted average of all the time window-specific results is calculated. The result of the analysis is presented by this weighted average of a series of relatively short-term effects (88,89).

Figure 7. Effect of time-varying risk in mortality

Friedo W. Dekker, *Kidney International*, 2008



This methodology has been used in the first part of the thesis, in order to assess the impact of the implementation of an assisted PD program in 2011. Indeed, the availability of the assistance varied depending on when the patient started KRT (before or after 2011).

2. Fractional polynomials

When investigating the association between a continuous variable and an outcome, it should be considered whether it is appropriate to include that variable as a linear term in the Cox regression model, and non-linearity should be tested. In case non-linearity is detected, the variable can be dichotomized in several categories. But this procedure requires to define category boundaries, which are often arbitrary and the process of categorisation leads to a loss of information because all cases within one category are treated as being equal. In order to avoid this loss of information, a smoothing non-linear association can be achieved either with splines or fractional polynomials (90–92).

A straightforward and flexible solution is to use a model that contains different powers of the same variable, a combination of polynomial (nonlinear transformation of the predictor variable) and logarithmic functions, referred to as fractional polynomials (FP) (90–93). For many applications, a first-degree FP is sufficient.

FP takes on the form $\beta_1 X^p$ with x being the predictor of interest, β_1 the beta coefficient and p the power of the polynomial, which may be fractional. The power is commonly chosen from $\{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}$. The convention is that X^0 equals $\ln(X)$. Second degree FPs can take one of two forms: (1) $\beta_1 X^p + \beta_2 X^q$ or (2) $\beta_1 X^p + \beta_2 X^q * \log(x)$, in order to find a combination of powers p and q that optimizes the model fit (89,90,94).

Considerable flexibility in modelling the impact of an explanatory variable on the hazard of a defined event can be achieved by using just one or two different powers of the variable. The several possibilities of powers are fitted in the model, and that with the smallest value of $-2\log$ of the maximised likelihood, in the presence of other explanatory variables, is the best fitting model (89,90,92).

3. Temporal trend analysis

The outcomes found in the epidemiological literature are frequently binary, and logistic regression is used. This results in the odds ratio being frequently reported in situation where incidence or prevalence ratio could be estimated. Of note the prevalence ratio, the ratio of the proportion of patients with an event over the proportion with the exposure, can be used in cross-sectional and longitudinal studies as a measure of the association between factors of exposition and an event of interest.

When working with frequent outcomes, with a proportion of events higher than 10%, the odds ratio can strongly overestimate the prevalence ratio. The relative risk interpretation

given to the odds ratio can be misleading and overestimated (95–97). In addition, interpreting the odds ratio as if it was a prevalence ratio is inadequate because confounding may not be appropriately controlled.

Several alternatives have been described in the literature for cross-sectional and longitudinal studies analysing binary outcomes, using the prevalence ratio rather than the odds ratio, notably by using a statistical model that estimates directly the prevalence ratio and its confidence interval. The most frequent models described in the epidemiological literature are Cox regression model with equal time of follow-up assigned to all individuals (98), log binomial regression (99,100) and Poisson regression (101,102). Barros *et al*, compared these three statistical models and concluded that Cox or Poisson regression with robust variance and log-binomial regression provided correct estimates and were a better alternative than logistic regression for the analysis of binary outcomes in cross-sectional and longitudinal studies (103).

As previously described, Cox regression estimates the hazard rate function that describes how the hazard rate depends upon several covariables.

$$H(t|X)=\exp(\beta' * X)*h_0(t)$$

where $h_0(t)$ is the baseline hazard function, X a vector of covariates and β' a vector of regression coefficients. In Cox regression, $h_0(t)$ is treated as a nuisance function and isn't actually estimated. The hazard ratio, a comparison between the probability of an event in an exposed group ($X=1$), compared to the probability of the same event in an unexposed group ($X=0$), and can be written as followed:

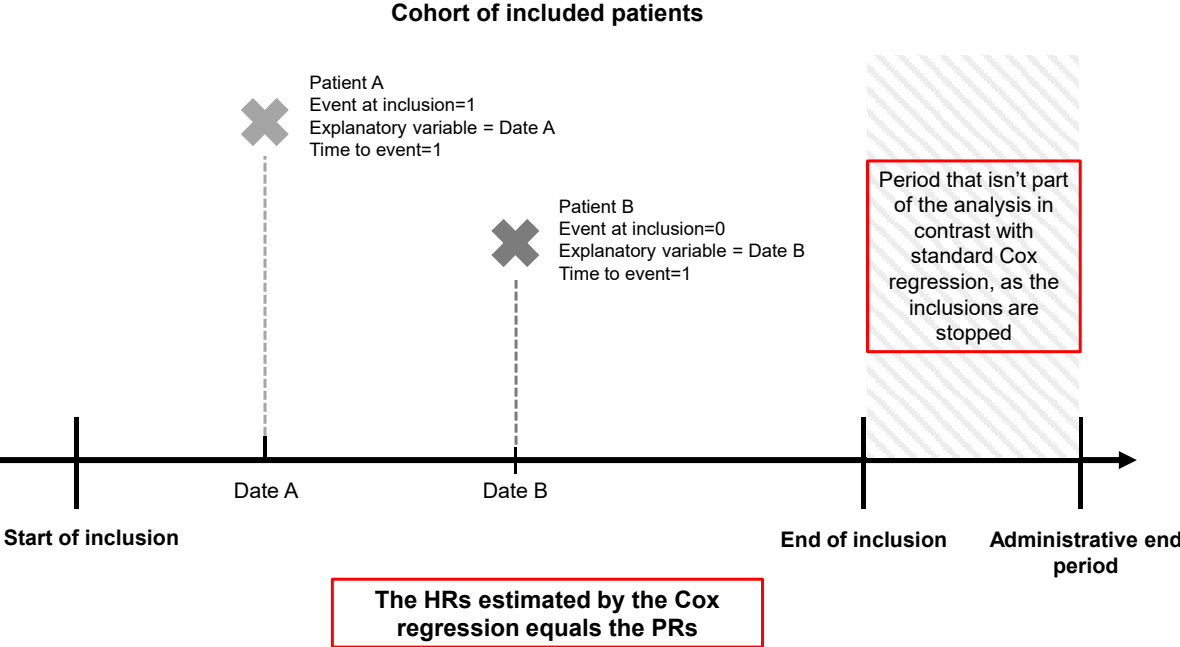
$$HR= [H(t|X=1)/ H(t|X=0)]=[(h_0(t)*\exp(\beta)]/ h_0(t) = \exp(\beta)$$

When a constant risk period (time to event (t) equals one) is assigned to every patient in the cohort, the hazard rate ratio estimated by the Cox regression equals the prevalence

ratio. However, the variance of the coefficients tends to be over-estimated, resulting in wider confidence intervals than those based on the binomial distribution (figure 8). An easy way to improve the situation is to use robust variance estimates, as proposed by Lin and Wei (104).

For the purpose of this work, Cox regression with robust variance has been used in order to describe longitudinal trends in PD usage and technique survival over the last decade.

Figure 8. Schematic of a cox regression with robust variance



4. Competing risk analysis

A competing risk is an event whose occurrence precludes the occurrence of the primary event of interest. For instance, in studies where the event of interest is death, patients may die from one of a number of different causes. In some cases, an analysis of death from all causes may be appropriate, using standard methods of survival analysis. However, as patients face death from a number of risks. These risks compete to become the actual cause of death and are defined as competing risks, in which a competing risk prevents the occurrence of an

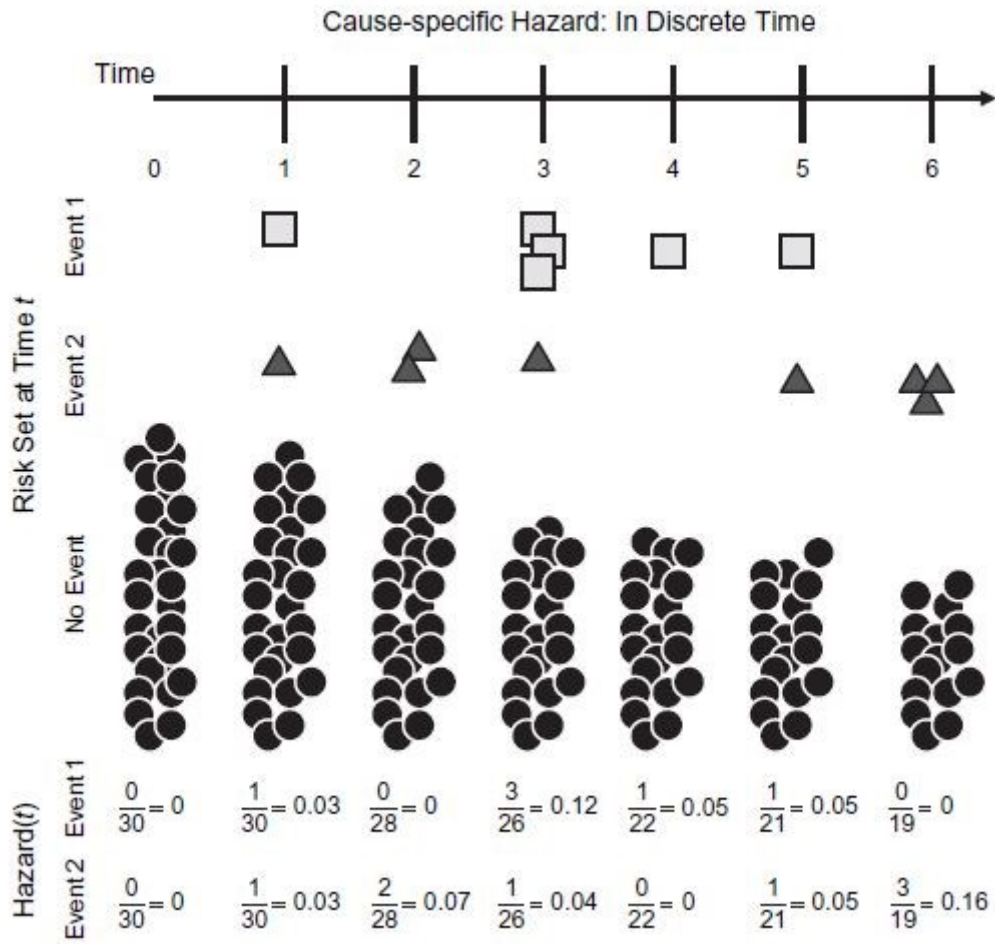
event of particular interest. More generally, competing risks applies when a patient may experience one of a number of different end-points, where the occurrence of any one of these eliminates the potential for others to occur.

The presence of competing risk has implications for the statistical analysis. The cause-specific hazard ratio (cs-HR) refers to the instantaneous rate of occurrence of a given event among the patients still event-free, whereas the cumulative incidence function is the probability of occurrence of a given event by time. Thus, the cumulative incidence expresses the expected proportion of patients with a certain event over time. The Kaplan-Meier survival curve, by disregarding censoring from competing event, may not appropriately estimate the cumulative incidence in the presence of competing events.

Competing risks are commonly analysed by using sub-distribution hazard ratio (sd-HR), also known as the Fine and Gray model. In standard survival analyses modelling cs-HR, the event times of patients who experience a competing risk are censored, and so are treated as if there is the possibility of the event of interest occurring in the future. As a consequence, the estimated cs-HR correspond to the situation where other causes of the event of interest are assumed not to occur, leading to the hazard of a particular cause of failure to be overestimated. The manner in which risk sets are defined in standard survival analyses may be modified to allow for competing events. In standard survival analysis, the risk set is defined as the group of individuals that have not experienced the outcome and therefore are at risk for the event of interest at time t , thus individuals who have a competing event are excluded from all later risk sets for the main event of interest, as illustrated in figure 9. In contrast, risk sets can be constructed in order to include both individuals without any event and those who have had a competing event (figure 10).

Figure 9. Cause-specific hazard ratio illustration

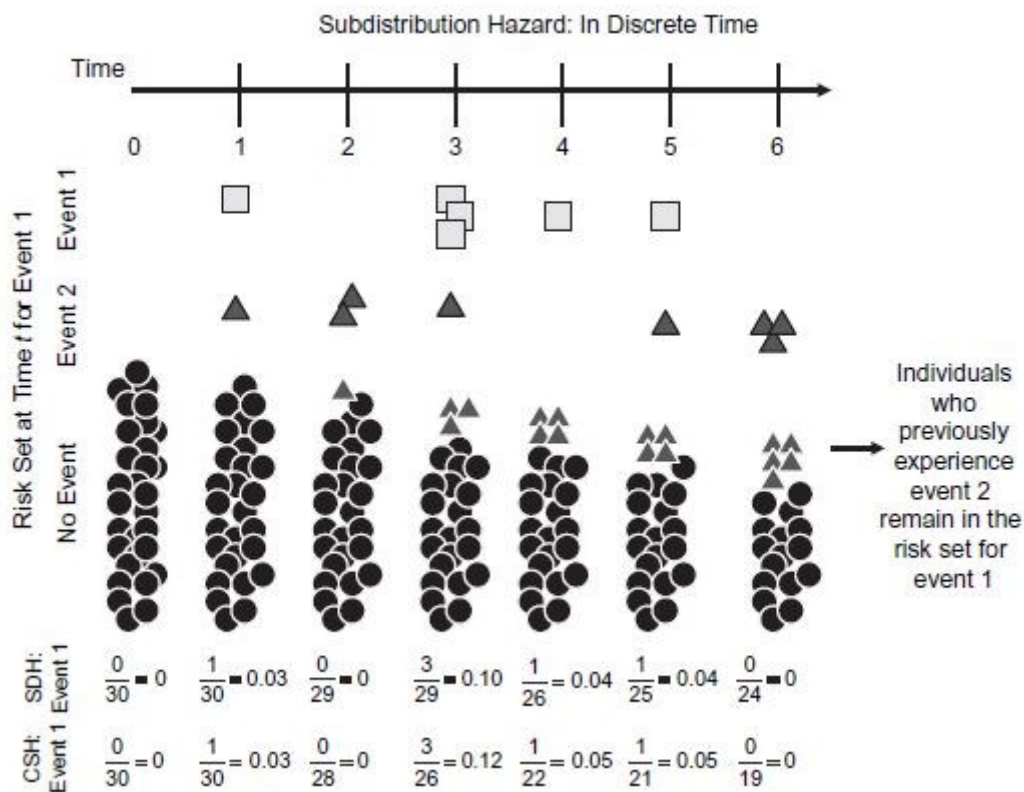
Lau Bryan, American Journal of Epidemiology, 2009



The risk set starts with 30 individuals (solid circles). Over time, individuals have either event 1 (square) or event 2 (triangle). As individuals have either event, they are removed from the remaining risk sets. The calculation for the cs-HR is given at the bottom of the figure.

Figure 10. Sub-distribution hazard ratio illustration

Lau Bryan, American Journal of Epidemiology, 2009



The risk set starts with 30 individuals (solid circles). Over time, individuals have either event 1 (square) or event 2 (triangle). As individuals have the competing event (event 2, triangle), they are maintained in the risk set as triangles. Thus, over time, a greater proportion of the risk set becomes full of triangles that are individuals who have had the competing event prior to that time. The sd-HR for event 1 is given near the bottom of the figure along with the cs-HR for event 1 for comparison. Note that, because individuals are maintained in the risk set, the sd-HR tends to be lower than the cs-HR.

Thus, for the cs-HR, the risk set decreases at each time point at which there is a failure for another cause (events that are not the events of interest are censored), measuring the specific association between the variable and the event of interest. For the sd-HR, the persons with failure from another cause remain in the risk set, assessing the net association between the variable and all possible events. The cs-HR may be better suited for studying the aetiology of diseases, when the sd-HR is useful in predicting an individual's risk (89,105–107).

5. Multiple imputation

Missing data occur in almost all medical studies. Its inadequate handling can lead to biased estimates of parameters resulting in incorrect confidence intervals and significance tests. Indeed, the absence of data reduces statistical power, which refers to the probability that the test will reject the null hypothesis when it is false. In addition, the lost data can cause bias in the estimation of parameters and reduce the representativeness of the samples. Each of these issues may threaten the validity of the study and lead to invalid conclusions (108).

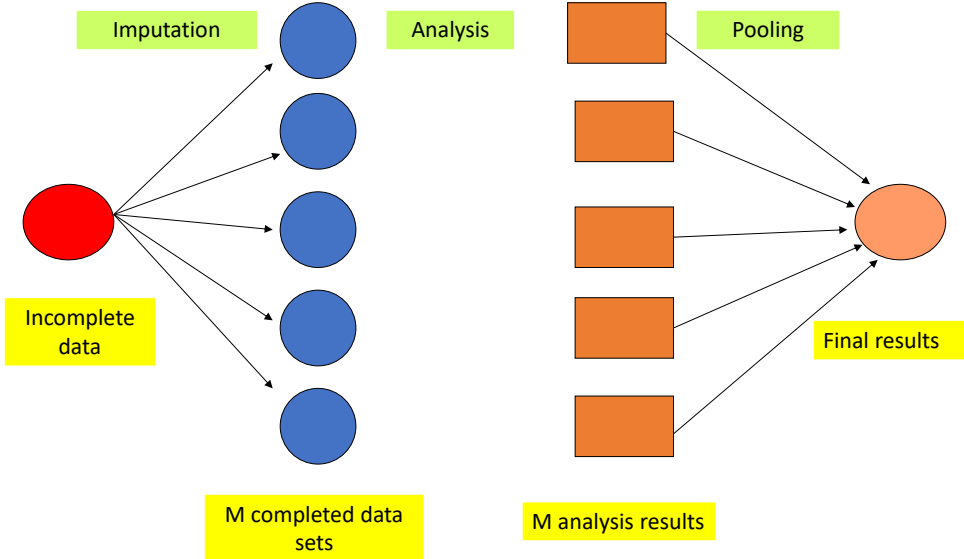
Missing data can be classified as being missing completely at random (MCAR—the probability of data being missing does not depend on the observed or unobserved data), missing at random (MAR—the probability of data being missing does not depend on the unobserved data, conditional on the observed data) or missing not at random (MNAR—the probability of data being missing does depend on the unobserved data, conditional on the observed data).

There are several ways to handle missing data. A complete case analysis removes all data for an observation that has one or more missing values, which can exclude a high number of patients depending on the proportion of missing data. Complete case analysis may be used if the potential impact of the missing data is negligible, and is classically used when the proportion of missing data is below approximately 5%. Another approach to handle this issue is to replace the missing data with estimated values, which is called imputation (109).

Multiple imputation (MI) has become increasingly popular. The key concept of MI is to use the distribution of the observed data to estimate a set of plausible values for the missing data. Instead of substituting a single value for each missing data, the missing values are replaced with a set of plausible values which contain the natural variability and uncertainty of the right values. The process starts with generating several imputed data sets, the unknown

missing data being replaced by m independent simulated sets of values estimated from the predictive distribution of the missing data conditional on the observed data. Secondly, each imputed data set is analysed separately. The parameters are estimated from each imputed data set, together with their variance–covariance matrices. The results of these m analyses differ as the missing values have been replaced by different imputations. Finally, the m estimates are combined using Rubin’s rules, to obtain the overall estimates, variances and confidence intervals. Figure 11 illustrates the several stages of MI (110,111).

Figure 11. The three stages of multiple imputation



Multiple imputation by chained equations (MICE), commonly used in case of missing values occurring in several variables, is based on a set of imputation models, one for each variable with missing values. In order to stabilize the results, the procedure is usually repeated for several cycles (e.g. 10 or 20) to produce a single imputed data set, and the whole procedure is repeated m times to give m imputed data sets. A linear regression model is the most

common choice for imputing normally distributed continuous variables, when logistic regression is usually chosen to impute binary variable. Categorical variables may be modelled either using multinomial logistic regression or using the proportional odds model. Standard texts on multiple imputation suggest that small numbers of imputed data sets ($m=3$ or 5) are adequate. However, larger numbers ($m=100$) of imputations may be required for method comparison studies (110).

III. Impact of the implementation of an assisted peritoneal dialysis program on peritoneal dialysis initiation

1. Introduction

As previously described, older people are the fastest growing group of patients with ESKD (22,79). Despite the many advantages' PD offers for the elderly and frail patient, its use has been declining in the past decade (22,76,77,79). One factor contributing to the decline in PD usage may be the increasing presence of social and medical conditions in the elderly patients that act as barriers to self-care PD.

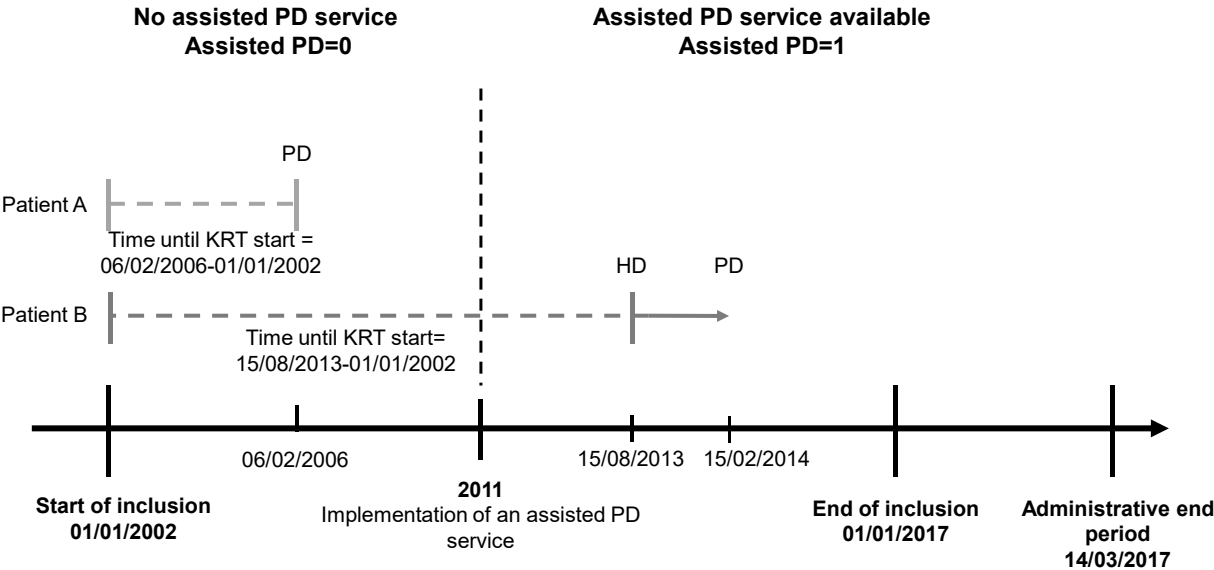
It has been demonstrated that assisted PD, by lifting some of these barriers, increases the number of patients eligible to PD (66). However, it is unclear what impact widespread adoption of assisted PD could have on PD initiation, with divided opinions in the nephrology community (112). Within the UK, there is no reliable data captured at a national level that would allow a reliable assessment of PD usage (22,77,79). One UK study examined practices associated with home dialysis use but the impact of assisted PD was not included in this (113).

The aim of the first part of the thesis, carried out with the data from Renal Unit of Royal Stoke University Hospital, was to assess the impact following the implementation in 2011 of an assisted PD service on the initiation of PD.

2. Materials and methods

Data from the Renal Unit of Royal Stoke University Hospital database was used for this study. All patients >18 years who began RRT at Royal Stoke University Hospital between 1 January 2002 and 1 January 2017 were included. Patients were followed from the start of any KRT until HD, PD or kidney transplant) until either PD initiation, death, transplant, transfer to another centre, recovery of renal function or administrative end period on 14 March 2017 (i.e. a pre-emptive transplant or starting KRT with PD would have an event time of 0 days and follow up stopped, whereas starting KRT with HD then transferring to PD, having a transplant or dying after 60 days would have an event time of 60 days and follow up stopped at that point), as illustrated in figure 12.

Figure 12. Methodology of the study



Cox proportional hazards model with assisted PD service modelled as a time varying covariate. Patient A: PD as first KRT, event time of 0 days and follow-up stopped. Patient B: HD as first KRT, event time of 6 months. PD: peritoneal dialysis, KRT: Kidney replacement therapy

Assistance was defined by the visit of a hospital employed and trained healthcare assistant to the patient once a day at home to set up the automated PD equipment for the session, with the patient only needing to connect their catheter and disconnect it afterwards. It was established locally, available from the start of 2011. Assistance provided by a family member was not considered as assisted PD.

The outcome of interest was PD initiation at any time after KRT start defined as an initiation of PD >1 day. Because availability of assisted PD varied depending on when a patient started KRT (e.g. available to all if starting after 2011, but after 2 years for those commencing in 2009), the primary analysis used a Cox proportional hazards

model, with availability of an assisted PD service as a time-varying explanatory variable, to estimate cs-HRs where the outcome was time to initiation of any form of PD. Secondary analyses included comparing two Cox models with KRT start year as exposure and the outcome self-care PD initiation only, or either of self-care or assisted PD initiation. This illustrates the effect of assisted PD availability on PD initiation (with self-care versus self-care and assisted) over time (figure 13). As death and transplantation rates were very likely to impact the cumulative incidence of PD initiation, these events were considered as competing events and sd-HR were estimated with a Fine and Gray regression.

Explanatory variables in regression analyses included KRT start year (length of time between 1 January 2002 and date of starting RRT), and comorbidities. The linearity for continuous explanatory variables (age and KRT start year) on cs-HRs and sd-HRs regression analysis was assessed with regression splines, and where necessary, FP and transformation to a categorical variable were explored.

Data were missing for four explanatory variables, with more than 10% missing values for two variables. A complete case analysis would have excluded 28% of the subjects from the dataset. MICE was performed, imputing 50 sets of missing values for the Cox regression models.

3. Results

Between January 2002 and 2017, 1576 patients incident to KRT were included in the study. Of these patients, 1126 (71%) started KRT with HD, 370 (24%) with PD, 80 (5%) with a pre-emptive transplant. 128 (8%) patients have been on assisted PD at some point and 723 started KRT while assisted PD was available. There were 1259 events during the study period:

482 (31%) PD initiation, 202 (13%) transplants and 575 (36%) deaths. Of the total PD initiations, 268 occurred before 2011, all starting with self-care PD and 26 (10%) moving to assisted PD when it became available; 214 occurred after 2011: 112 (52%) started self-care PD with 32 moving to assisted PD later and 102 (48%) patients started assisted PD with 35 moving to self-care PD later. The KRT population was aging during the study period, with the PD population aging at a faster rate, as illustrated in table 4.

Assisted PD service availability was associated with an increased rate of PD initiation (cs-HR 1.78, 95% confidence interval (95% CI) 1.21-2.61), as described in table 5. The analysis with KRT start year expressed as a linear term provided similar results (cs-HR 1.98, 95% CI 1.39-2.81).

Table 4. Description of the age according to KRT and PD characteristics

Population	Median age (IQR)
KRT initiation	
Before 2011	66.2 years (IQR 50.6– 74.7)
After 2011	67.7 years (IQR 55.8– 77.35)
PD initiation	
Before 2011	59.4 years (IQR 45.8–70.2)
After 2011	65.3 years (IQR 51.6–74.1)
Assistance status at PD initiation	
No assistance	58.7 years (IQR 43.8–69.2)
Assistance	70.0 years (IQR 61.5–78.3)

Table 5. Association between the availability of assisted PD and the hazard rate of PD initiation, adjusting for patient characteristics.

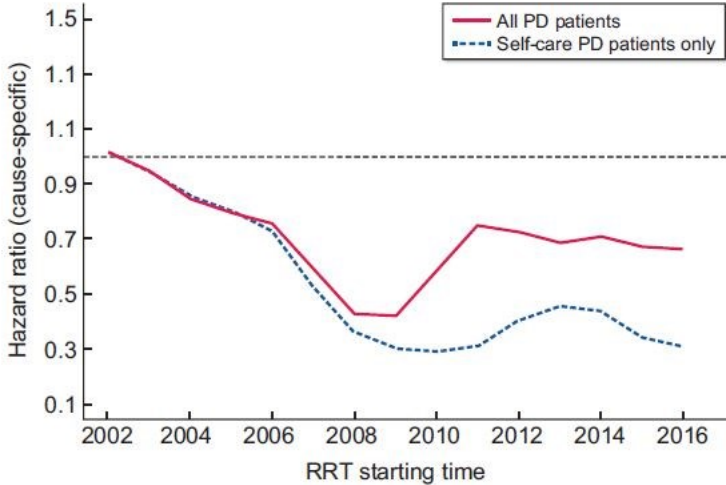
Explanatory variable	cs-HR (95% CI)
Assisted PD availability	1.78 (1.21–2.61)*
RRT starting time (FP) ^a	$x + x^2$ **
Age (per 10-year increase)	
Male	0.76 (0.70–0.82)**
Female	0.64 (0.54–0.77)**
Gender	
Female	Reference
Male	0.39 (0.20–0.74)*
Ethnicity	
White	Reference
Non-white	0.97 (0.65–1.43)
Primary renal disease	
Diabetes	Reference
Glomerulonephritis	0.89 (0.66–1.20)
Renal vascular disease	0.96 (0.71–1.29)
Polycystic	1.07 (0.73–1.56)
Pyelonephritis	0.89 (0.59–1.33)
Uncertain aetiology	1.14 (0.83–1.57)
Other	0.59 (0.42–0.83)*

Adjusted analysis with a time-varying explanatory variable Cox regression model. aRRT starting time expressed as FP: initial decrease of the cs-HR of PD initiation. From 2014, the curve flattened, corresponding to a stabilization in PD initiation rates at a cs- HR of 0.33. *P < 0.01, **P < 0.001.

In the analysis including assisted PD as an outcome, more recent KRT start year was strongly associated with the reduction in initiation of PD, whether included in the model as a categorical explanatory variable (figure 13) or a fractional polynomial (figure 14). As shown in

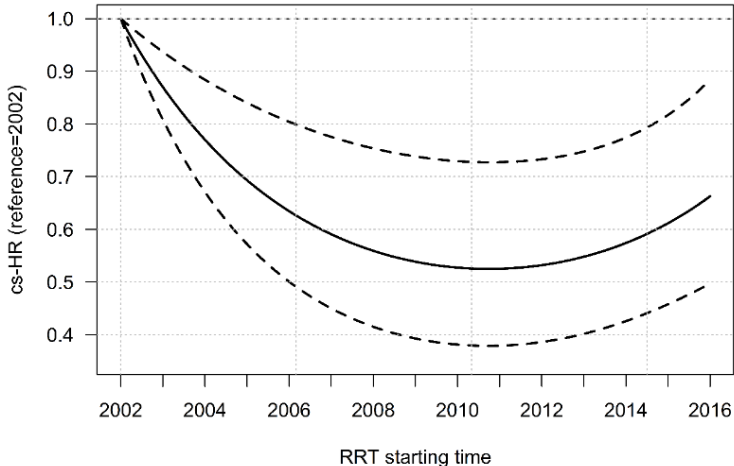
figure 13, the cs-HR evolution over time followed a similar pattern as when assisted PD was included in the event of interest, but the curves diverge sharply when the assisted PD service was introduced and then stay approximately parallel. In both models, the decreasing hazard rates of starting PD flattened from 2010, with an average cs-HR of 0.60 when including assisted PD compared to an average cs-HR of 0.40 when excluding assisted PD.

Figure 13. Effect of assisted PD service on the hazard rate of PD initiation over time



Change in the proportional use of PD over time: lines (solid line: all PD patients, dashed line: self-PD patients only) represent the rates of receiving PD at any point during follow-up, by the year that kidney replacement therapy was initiated, compared with 2002 (expressed as an HR). The analysis was adjusted for age, gender, ethnicity, and primary renal disease using a Cox regression. When excluding patients starting assisted PD from the outcome of interest, the cs-HR evolution over time followed a similar pattern as when assisted PD was included in the event of interest, but the curves diverge sharply when the assisted PD service was introduced and then stay approximately parallel. In both models, the decreasing hazard rates of starting PD flattened from 2010, with an average cs-HR of 0.60 when including assisted PD compared with an average cs-HR of 0.40 when excluding assisted PD. This illustrates the effect of assisted PD availability on PD initiation.

Figure 14. Effect of time on the rate of PD initiation



Adjusted for age, gender, ethnicity and primary kidney disease. Effect of time modelled by fractional polynomial regression. All PD patients included, irrespective of need for assistance. Solid line: cs-HR, dashed lined: 95% CI.

Transplantation and death rates increased over time but this did not affect the fall in PD initiation (for each year in the study cs-HR of starting PD 0.95 [0.93-0.98], sd-HR 0.95 [0.94-0.97]). The results of the adjusted analysis for Cox and competing risks regression are shown in Table 6. If transplantation only was considered as a competing event to PD initiation, the sd-HR for RRT start year to PD initiation rose to 0.96 (95% CI 0.94–0.97), as well as to transplant, 1.04 (95% CI 1–1.08).

Table 6. Adjusted cs-HRs (Cox model) and sd-HR (Fine and Gray model) for each event

Explanatory variable	PD		Transplant		Death	
	cs-HR (95% CI)	sd-HR (95% CI)	cs-HR (95% CI)	sd-HR (95% CI)	cs-HR (95% CI)	sd-HR (95% CI)
RRT starting time (linear, for a 1-year increase)	0.95 (0.93–0.98)***	0.95 (0.94–0.97)***	1.07 (1.02–1.12)**	1.03 (0.99–1.07)	1.03 (1–1.07)	0.98 (0.95–1)
Age (for a 10-year increase)	0.85 (0.80–0.90)***	0.88 (0.83–0.92)***	0.48 (0.43–0.54)***	0.53 (0.49–0.58)***	1.60 (1.44–1.77)***	1.89 (1.72–2.08)***
Gender						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	0.99 (0.81–1.21)	1 (0.84–1.19)	1.46 (1–2.10)	0.62 (0.43–0.89)*	1.02 (0.81–1.27)	1.16 (0.93–1.45)
Ethnicity						
White	Reference	Reference	Reference	Reference	Reference	Reference
Non-white	1 (0.69–1.48)	1 (0.72–1.39)	1.08 (0.62–1.86)	1.16 (0.69–1.95)	0.85 (0.49–1.46)	0.74 (0.44–1.26)
Primary renal disease						
Diabetes	Reference	Reference	Reference	Reference	Reference	Reference
Glomerulonephritis	0.84 (0.61–1.15)	0.87 (0.67–1.13)	1.15 (0.67–1.99)	1.47 (0.85–2.55)	0.52 (0.35–0.77)***	0.59 (0.41–0.85)**
Renal vascular disease	0.94 (0.68–1.29)	0.96 (0.73–1.27)	0.79 (0.37–1.66)	0.85 (0.40–1.79)	0.72 (0.53–0.99)*	0.71 (0.53–0.96)*
Polycystic	1 (0.68–1.47)	1 (0.72–1.39)	2.94 (1.68–5.13)***	3.65 (2.15–6.20)***	0.26 (0.11–0.58)**	0.22 (0.10–0.50)***
Pyelonephritis	1.08 (0.72–1.60)	1.04 (0.75–1.44)	1.16 (0.53–2.54)	1 (0.42–2.39)	0.71 (0.44–1.14)	0.70 (0.44–1.12)
Uncertain aetiology	1.16 (0.84–1.62)	1.16 (0.87–1.53)	1.30 (0.67–2.53)	1.32 (0.68–2.55)	0.92 (0.62–1.37)	0.61 (0.41–0.88)*
Other	0.60 (0.42–0.86)**	0.63 (0.46–0.87)**	1.17 (0.66–2.08)	1.32 (0.75–2.29)	1.07 (0.77–1.48)	1.30 (0.92–1.82)

*P < 0.05, **P < 0.01, ***P < 0.001

4. Discussion

We have provided the first description of the impact of the provision of an assisted PD service on PD usage, in a UK centre. We observed an approximately 80% increase in the uptake, reducing the fall in PD rates over time. These changes appear to be independent of changes in competing events over time. As expected, older patients seemed to benefit most from the assistance program.

Another important finding of our study is that the positive impact on PD initiation has been perceived one to two years after implementing the assisted PD service (figure 14). When implementing such a service, practitioners shouldn't expect an immediate uptake in PD initiation, as some time is required before expected benefits to be perceived. Assisted PD services need to be monitored closely to maximize their impact, so that their use remain stable over time.

The implications of our study are that widespread adoption of the provision of an assisted PD program would significantly increase PD initiation, particularly providing PD as an option for older and frailer patients. However, our study does not demonstrate the impact on prevalence. Assistance has been associated with a lower risk for technique failure or transplantation (114), but a higher risk for death as the patients were older and frailer. So it is possible that developing assisted PD services will increase PD prevalence, but mortality rates are likely to be high given the older and frailer population.

This first study enabled us to highlight the importance of developing assisted PD programs. Our findings could be an argument in favour of economic incentives in order to further promote assisted PD. Some countries, such as France, have introduced strategic economic incentives to increase home dialysis usage. However, there is limited information available on the use of assisted PD over time and the impact of economic incentives on its utilization. This statement led us to carry on further investigations.

5. Article

Impact of the implementation of an assisted peritoneal dialysis service on peritoneal dialysis initiation

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ABSTRACT

Background. There is limited information available on the impact that provision of an assisted peritoneal dialysis (PD) service has on the initiation of PD. The aim of this study was to assess this impact in a centre following initiation of assisted PD in 2011. **Methods.** This retrospective, single-centre study analysed 1576 patients incident to renal replacement therapies (RRTs) between January 2002 and 2017. Adjusted Cox regression with a time-varying explanatory variable and a Fine and Gray model were used to examine the effect of assisted PD use on the rates and cumulative incidence of PD initiation, accounting for the non-linear impact of RRT starting time and the competing risks (transplant and death). **Results.** Patients starting PD with assistance were older than those starting unassisted: median (interquartile range): 70.0 (61.5–78.3) versus 58.7 (43.8–69.2) years old, respectively. In the adjusted analysis assisted PD service availability was associated with an increased rate of PD initiation [cause-specific hazard ratio (cs-HR) 1.78, 95% confidence interval 1.21–2.61]. During the study period, the rate of starting PD fell before flattening out. Transplantation and death rates increased over time but this did not affect the fall in PD initiation [for each year in the study cs-HR of starting PD 0.95 (0.93–0.98), sub-distribution HR 0.95 (0.94–0.97)].

Conclusions. In a single-centre study, introducing an assisted PD service significantly increased the rate of PD initiation, benefitting older patients most. This offsets a fall in PD usage over time, which was not explained by changes in transplantation or death.

Keywords: assisted peritoneal dialysis, chronic kidney disease, peritoneal dialysis, renal replacement therapy

INTRODUCTION

Older people are the fastest growing group of patients with end-stage renal disease (ESRD) [1, 2]. For patients requiring renal replacement therapy (RRT), transplantation is associated with

better outcomes [3, 4] and quality of life [5–7], and lower costs [8], but it is not possible for all patients, particularly the elderly or frail [9].

Peritoneal dialysis (PD) has been associated with a better quality of life [10–12], better outcomes in the first 2–3 years [13–17] and lower costs than haemodialysis (HD) [18, 19]. As a home therapy, it offers several advantages for elderly patients with comorbidities. Most important are the avoidance of transport to and from the dialysis unit, difficult vascular access and haemodynamic instability during HD sessions [20, 21]. The conditions that act as a barrier to self-care PD in the elderly can be overcome by assisted PD [22, 23]. Assistance can thus improve accessibility of home dialysis and survival in elderly or frail patients [22, 24, 25], whose quality of life may benefit most from home care dialysis [11].

Despite these advantages, use of PD has been declining in the past decades [1, 2, 26, 27], e.g. in the UK the PD prevalence in 2015 was of 55 per million population, a reduction of 6.2% compared with 2005 [2, 27]. It is unclear what impact widespread adoption of assisted PD could have on this, with divided opinions in the nephrology community [28]. Assisted PD usage varies between European countries, according to the health care reimbursement system [24, 25]. Within the UK, there is no reliable data captured at a national level that would allow a reliable assessment [1, 2, 27]. One UK study examined practices associated with home dialysis use but the impact of assisted PD was not included in this [29].

The aim of this study is to assess the impact of the implementation of an assisted PD service on PD initiation.

MATERIALS AND METHODS

Study population

This retrospective, single-centre study used the data from the Renal Unit of Royal Stoke University Hospital database. All patients >18 years who began RRT at Royal Stoke University Hospital between 1 January 2002 and 1 January 2017 were included. Patients were followed from the start of any RRT until

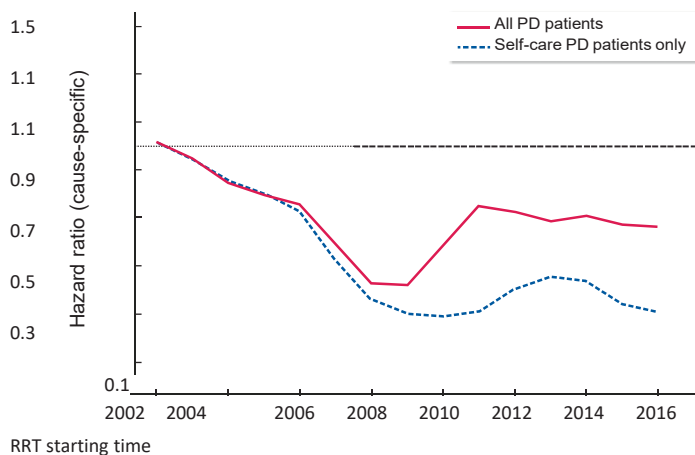


FIGURE 1: Effect of assisted PD service on the hazard rate of PD initiation over time. Change in the proportional use of PD over time: lines (solid line: all PD patients; dashed line: self-care PD only) represent the rates of receiving PD at any point during follow-up, by the year that renal replacement was initiated, when compared with 2002 (expressed as an HR). The analysis was adjusted for age, gender, ethnicity and primary renal disease using a Cox model. There is a relative reduction in PD use between 2002 and 2008 that is partially reversed in after the introduction of assisted PD in 2011, at which point PD use stabilized.

PD initiation, death, transplant, transfer to another centre, recovery of renal function or administrative end period on 14 March 2017 (i.e. a pre-emptive transplant or starting RRT with PD would have an event time of 0 days and follow-up stopped, starting RRT with HD then transferring to PD, having a transplant or dying after 60 days would have an event time of 60 days and follow-up stopped at that point). No patients were lost to follow-up. Patients transferred in from another hospital were excluded.

Assisted PD service

Hospital-employed and trained healthcare assistants visit the patient once a day at home to set up the automated PD equipment for the session, with the patient only needing to connect their catheter and disconnect it afterwards. It was established locally, available from the start of 2011. Support is provided to all patients thought to benefit, as decided in discussion between a home dialysis nurse and the patient, for as long as necessary. The healthcare assistants clean exit sites, help weigh patients and liaise with the home dialysis nurse for troubleshooting as required. Assistance provided by a family member was not considered as assisted PD. After introduction, the service was monitored to ensure it was sustained over time. The increased cost is now reflected in the national tariff for dialysis, introduced a year after initiation of the service.

Patient characteristics

These included age at RRT start, gender, ethnicity, primary renal disease and assisted PD availability. The primary renal disease was composed of the following classes: diabetes, glomerulonephritis, vascular renal disease, polycystic, pyelonephritis, uncertain aetiology and others. The latter included all

nephropathies that did not belong to one of the previous classes, such as myeloma kidney and acute kidney injury.

Statistical analysis

The outcome of interest was PD initiation at any time after RRT start defined as an initiation of PD >1 day and in a comparative analysis as PD treatment lasting at least 90 days. Continuous variables are described by their median [interquartile range (IQR)], and categorical variables by frequency and percentage. Because availability of assisted PD varied depending on when a patient started RRT (e.g. available to all if starting after 2011, but after 2 years for those commencing in 2009), the primary analysis used a Cox proportional hazards model, with availability of an assisted PD service as a time-varying explanatory variable [30, 31], to estimate cause-specific hazard ratios (cs-HRs) where the outcome was time to initiation of any form of PD. Secondary analyses included comparing two Cox models with RRT start year as exposure and the outcome self-care PD initiation only, or either of self-care or assisted PD initiation. This illustrates the effect of assisted PD availability on PD initiation (with self-care versus self-care and assisted) over time (Figure 1). A Fine and Gray model, with a primary outcome of any PD initiation and competing events of transplantation and death, was also used to assess the impact competing events could have on the cumulative incidence of PD initiation. All analyses were repeated with PD usage defined as >90 days of PD treatment.

Explanatory variables in regression analyses included RRT start year (length of time between 1 January 2002 and date of starting RRT), age at RRT start, gender, ethnicity and primary renal disease. The linearity for continuous explanatory variables (age and RRT start year) on cs-HRs and sub-distribution HRs (sd-HRs) regression analysis was assessed with regression splines, and where necessary, fractional polynomial (FP) and transformation to a categorical variable were explored [32]. Interactions were tested in all multivariable models. Proportionality assumptions were assessed with Schoenfeld residual and log-minus-log plots.

Data were missing for four explanatory variables, with more than 10% missing values for two variables. A complete case analysis would have excluded 28% (448 patients) of the subjects from the dataset. Multiple imputation by chained equation (MICE) was performed, imputing 50 sets of missing values for the Cox regression models. All statistical analyses were performed with R 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria; the 'mprs' library was used to fit the Fine and Gray regression models).

RESULTS

Patient characteristics

Of the 1698 patients starting RRT after 2002, 91 were transferred in from another hospital and 31 were aged <18 years; 1576 patients were included in the analyses (Figure 2). Of these patients, 1126 (71%) started RRT with HD, 370 (24%) with PD and 80 (5%) with a pre-emptive transplant. Some 128 patients

(8%) have been on assisted PD at some point and 723 started RRT while assisted PD was available.

The median time to PD initiation was 0 months (IQR 0–61 days). There were 1259 events during the study period: 482 (31%) PD initiation, 202 (13%) transplants and 575 (36%) deaths. If PD initiation was defined as at least 90 days of treatment, 465 (30%) patients started PD, 205 (13%) had a transplant and 589 (37%) died. Of the total PD initiations, 268 occurred before 2011, all starting with self-care PD and 26 (10%) moving to assisted PD when it became available; 214 occurred after 2011: 112 (52%) started self-care PD with 32 moving to assisted PD later and 102 (48%) patients started assisted PD with 35 moving to self-care PD later.

Patient characteristics are described in [Table 1](#), with further detail on those receiving assisted PD in [Table 2](#). [Table 3](#) describes the number of patients starting PD and assisted PD by year of RRT start. The RRT population was aging during the study period, with the PD population aging at a faster rate: the RRT population had a median age of 66.2 years (IQR 50.6–74.7) if starting RRT before 2011 versus 67.7 years (IQR 55.8–77.35) if starting RRT after 2011, a difference of 1.6 years. The PD population had a median age of 59.4 years (IQR 45.8–70.2) if starting before 2011 versus 65.3 years (IQR 51.6–74.1) if starting after 2011, a difference of 5.9 years. Patients starting PD with assistance were significantly older than those starting un-assisted: the median age of patients starting PD without assistance was 58.7 years (IQR 43.8–69.2) versus 70.0 years (IQR 61.5–78.3) with assistance.

Assisted PD availability as a time-varying explanatory variable

Adjusting for the other explanatory variables, assisted PD service being available was strongly associated with an increased rate of PD initiation [cs-HR 1.78, 95% confidence interval (95% CI) 1.21–2.61]. The RRT start year, age, male gender and primary renal disease ‘other’ were associated with the outcome. The interaction between gender and age was significant, with the difference between males and females becoming smaller for each year older ([Table 4](#)). The analysis with RRT start year expressed as a linear term provided similar results (cs-HR 1.98, 95% CI 1.39–2.81).

PD initiation rates over time with and without assisted PD

In the analysis including assisted PD as an outcome, more recent RRT start year was strongly associated with the reduction in initiation of PD, whether included in the model as a categorical explanatory variable ([Figure 1](#)) or an FP ([Supplementary data, Figure S1](#) and [Table S1](#)).

When excluding patients starting assisted PD from the outcome of interest, only 356 patients (22%) started PD during the study period. As shown in [Figure 1](#), the cs-HR evolution over time followed a similar pattern as when assisted PD was included in the event of interest, but the curves diverge sharply when the assisted PD service was introduced and then stay approximately parallel. In both models, the decreasing hazard rates of starting PD flattened from 2010, with

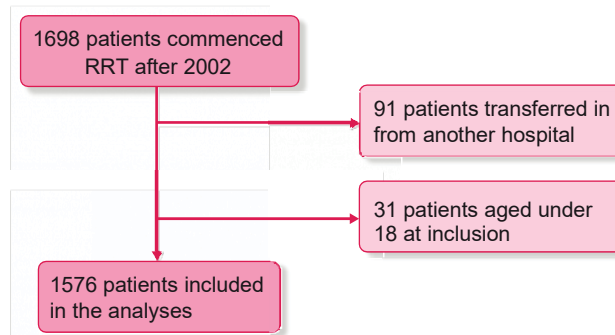


FIGURE 2: Flowchart of patient inclusion in analysis.

an average cs-HR of 0.60 when including assisted PD compared with an average cs-HR of 0.40 when excluding assisted PD. This pattern is also observed when considering 95% confidence regions for the cs-HRs as shown in [Supplementary data, Figure S2](#).

Impact of changes in competing events on PD initiation

In unadjusted Cox regression models, RRT start year (linear term) was associated with a decreased rate of PD initiation and death and an increased rate of transplantation, with a cs-HR for each 1-year increase of 0.97 (95% CI 0.95–0.99), 0.98 (95% CI 0.96–0.99) and 1.08 (95% CI 1.04–1.13), respectively.

In unadjusted competing risks models, the RRT start year was associated with a decreased cumulative incidence of PD initiation and death and a higher cumulative incidence of transplant [sd-HR for 1-year increase of 0.97 (95% CI 0.95–0.99), 0.95 (95% CI 0.93–0.97) and 1.05 (95% CI 1.02–1.08), respectively]. The results of the adjusted analysis for Cox and competing risks regression are shown in [Table 5](#). If transplantation only was considered as a competing event to PD initiation, the sd-HR for RRT start year to PD initiation rose to 0.96 (95% CI 0.94–0.97), as well as to transplant, 1.04 (95% CI 1–1.08).

For all models, comparative analyses defining PD initiation as PD treatment lasting over 90 days provided equivalent results, so are not described further.

DISCUSSION

We have provided the first description of the impact of the provision of an assisted PD service on PD usage in a UK centre, with an 80% increase in the uptake, reducing the fall in PD rates over time. These changes appear to be independent of changes in competing events over time, and of changes in age, gender, ethnicity and primary renal disease. Older patients seemed to benefit most from the assistance service.

The change was greatest in the year the assisted service was introduced, which has now settled down to a slightly lower steady state of assisted PD use ([Table 3](#)).

In the UK, there is significant variation between centres in the use of PD, largely driven by differences in the proportions initiating dialysis with PD, which ranges from 6.3% to 49.7% [27]. Some of this centre variation may be due to different approaches to the provision of assisted PD. In the UK, assisted PD generally refers to when a healthcare professional provides

Table 1. Patient characteristics

Variable	All patients (n=1576)	All PD patients (n=482)	Assisted PD (n=128)	Self-care PD (n=354)
Age, years, median (IQR)	66.7 (52.9–75.9)	62.6 (48.1–1.6)	70 (61.5–78.3)	58.7 (43.8–69.2)
Gender (male) n (%)	961 (61)	295 (61)	84 (66)	211 (60)
RRT starting year, median (IQR)	2010 (2007–14)	2010 (2005–14)	2013 (2011–15)	2007 (2004–13)
Ethnicity, n (%)				
White	1127 (72)	393 (82)	102 (80)	291 (82)
Non-white	86 (5)	30 (6)	7 (5)	23 (7)
Missing	363 (23)	59 (12)	19 (15)	40 (11)
Primary renal disease, n (%)				
Diabetes	352 (22)	119 (25)	35 (27)	84 (24)
Glomerulonephritis	222 (14)	73 (15)	11 (8)	62 (17)
Renal vascular disease	255 (16)	73 (15)	27 (21)	46 (13)
Polycystic	99 (6)	38 (8)	4 (3)	34 (10)
Pyelonephritis	97 (6)	32 (6)	1 (1)	31 (9)
Uncertain aetiology	158 (10)	61 (13)	18 (14)	43 (12)
Other	227 (15)	49 (10)	16 (13)	33 (9)
Missing	166 (11)	37 (8)	16 (13)	21 (6)
Modality at end of follow-up, n (%)				
PD	64 (4)	64 (14)	29 (22)	35 (10)
Assisted PD	26 (2)	26 (6)	26 (20)	0 (0)
Self-care PD	38 (2)	38 (8)	3 (2)	35 (10)
HD	308 (20)	45 (9)	13 (10)	32 (9)
Transplant	282 (18)	112 (23)	6 (5)	106 (30)
Recovered renal function	45 (3)	9 (2)	3 (2)	6 (2)
Transferred out	51 (3)	15 (3)	2 (2)	13 (4)
Deceased	826 (52)	237 (49)	75 (59)	162 (45)

Continuous variables are reported as the median (first and third quartile); categorical variables are reported as frequencies and percentage.

assistance, and family members providing assistance is usually recorded as self-care PD. Usually, the trained healthcare assistant will set up the automated PD equipment, but not connect or disconnect the PD catheter to the machine. Assisted PD can be used in different ways, for example as a temporary measure during the training period before becoming independent, either in the context of acute start PD or where the patients and their carers lack confidence, or as a permanent measure for elderly patients who have barriers to self-care PD [29]. In France, Canada and the Netherlands, assistance is provided by a community nurse or a trained family member, who will connect and disconnect the catheter to the machine, and it can be used for continuous ambulatory PD as well as automated PD [22–25]. It is not clear what other models are used internationally. The type of assistance, either by a trained health-care or a family member, is not always provided in national registers, making national and international comparisons difficult.

It would be anticipated that provision of an assisted PD service, by removing some of the barriers to home dialysis, should increase the number of patients eligible for PD. In one Canadian study, availability of home-care assistance was associated with an odds ratio of 1.4 for PD usage, but the numbers in this study were smaller (134 incident patients), with significant imprecision in the effect estimate making the results highly uncertain. Our study, considering 723 patients incident to RRT while assisted PD was available, provides greater precision in the effect estimate. The relative effect of assisted PD availability will also vary according to the absolute rate of PD usage, and during the Canadian study ~37% of patients started PD with-out assistance, compared with ~20% in our study [22]. In a

Table 2. Description of how assisted PD was received

Variable	Assisted PD (n=128)
PD starting year, median (IQR)	2013 (2011–2015)
Proportion receiving self-care PD before assistance, n (%)	26/26 (100)
PD initiation before 2011, ^a n (%)	32/102 (31)
PD initiation after 2011, n (%)	22.2 (10.5–35.7)
Months ^b of self-care PD before assistance, median (IQR)	41.9 (26.6–58.3)
PD initiation before 2011 ^a	1.28 (0.33–7.34)
PD initiation after 2011	3.98 (0.84–19.25)
Months of assistance, median (IQR)	3.98 (0.84–19.25)
Next recorded modality, n (%)	
PD	

Continuous variables are reported as the median (first and third quartile); categorical variables are reported as frequencies and percentage.

^aPD initiation before 2011 was only self-care PD as the assistance service was not available.

^bDuration in months of patients who had self-care PD before assistance.

more recent study from the same centre, in a region where all patients had access to assistance, the impact of family support on PD utilization was assessed. Family support was associated with a significant increase in PD eligibility, from 63% to 80% in patients with barriers to self-care PD, and an increase in choice of PD (40–57%), resulting in an increase in PD utilization from 23% to 39% (P=0.009) [23].

Table 3. Number of patients at risk, starting PD and having assisted PD by year of RRT start

RRT starting year	Number of patients		
	Starting assisted RRT	Starting PD, ^a n (%)	Starting PD, ^b n (%)
2002	88	44 (50)	0 (0)
2003	74	31 (42)	2 (3)
2004	102	40 (39)	0 (0)
2005	74	25 (34)	1 (1)
2006	86	32 (37)	1 (1)
2007	96	27 (28)	5 (5)
2008	98	19 (19)	2 (2)
2009	128	22 (17)	5 (4)
2010	107	28 (26)	10 (9)
2011	105	40 (38)	30 (29)
2012	84	26 (31)	7 (8)
2013	127	34 (27)	10 (8)
2014	130	44 (34)	17 (13)
2015	139	34 (25)	19 (14)
2016	138	36 (26)	19 (14)

Values are expressed as the number (percentage) of all patients.

^aNumber of patients starting PD (including assisted PD), over the study period, by RRT starting year.

^bNumber of patients starting assisted PD, over the study period, by RRT starting year.

The prevalence of PD has been declining in the UK in recent decades, albeit with wide variation between centres [1, 2, 27, 29]. Our centre is following a similar pattern, although the decline seems to have arrested, with the adjusted Cox regression results indicating that the proportion of patients initiating PD remained approximately the same since 2010, independent of the introduction of the assisted service. The assisted PD service did not have a significant impact on PD usage, causing a sharp increase at the time of introduction with this higher rate being maintained once the service was established. This is illustrated graphically in Figure 1. Assisted PD services need to be monitored closely to maximize their impact, so that their use remains stable over time. Of note, the program did not help with connection to cyclers, which may have limited its impact.

Transplantation, as shown by the adjusted Cox model, increased over the study period, whilst death rates may have decreased slightly. Accounting for the overall effect of these two competing events with a Fine and Gray model did not change the impact of start year on PD initiation [sd-HR 0.95 (0.94–0.97) compared with cs-HR 0.95 (0.93–0.98); Table 5]. Rising transplant rates have been thought to explain some of the fall in PD usage in the UK, but this analysis suggests that competing events are not the primary driver in our centre.

Older age was also associated with a decreased probability for PD initiation, likely a reflection of increased comorbidity, frailty and dependency. Similar findings have been described in the Netherlands: patients aged >70 years old were six times more likely to choose HD over PD than patients aged between 18 and 40 years [33]. In the UK, age was associated with a 2% decrease in odds of choosing PD therapy [34]. The effect of age was not consistent between the genders, with older age decreasing the chance of starting PD more in females. Similar results have been observed nationally [1, 2, 27], although the explanation for this phenomenon is not clear. In our study, older

Table 4. Association between the availability of assisted PD and the hazard rate of PD initiation, adjusting for patient characteristics

Explanatory variable	cs-HR (95% CI)
Assisted PD availability	1.78 (1.21–2.61)*
RRT starting time (FP) ^a	$x + x^2$ **
Age (per 10-year increase)	
Male	0.76 (0.70–0.82)**
Female	0.64 (0.54–0.77)**
Gender	Reference
Female	Reference
Male	0.39 (0.20–0.74)*
Ethnicity	
White	Reference
Non-white	0.97 (0.65–1.43)
Primary renal disease	
Diabetes	Reference
Glomerulonephritis	0.89 (0.66–1.20)
Renal vascular disease	0.96 (0.71–1.29)
Polycystic	1.07 (0.73–1.56)
Pyelonephritis	0.89 (0.59–1.33)
Uncertain aetiology	1.14 (0.83–1.57)
Other	0.59 (0.42–0.83)*

Adjusted analysis with a time-varying explanatory variable Cox regression model.

^aRRT starting time expressed as FP: initial decrease of the cs-HR of PD initiation. From 2014, the curve flattened, corresponding to a stabilization in PD initiation rates at a cs-HR of 0.33.

* $p < 0.01$, ** $p < 0.001$.

patients seemed to benefit most from the availability of assistance—patients who probably would not have started PD otherwise. Experience in the unit suggests that assisted PD was also of benefit to patients who would previously have started straight self-care PD, where assisted PD allowed a more rapid discharge and/or provided an extended training period (27% of patients moved from assisted to self-care PD). This approach evolved over time, possibly explaining a slight increase in the proportion using assisted PD between 2012 and 2016.

The implications of our study are that widespread adoption of the provision of an assisted PD service would significantly increase PD initiation, particularly providing PD as an option for older, frailer patients, but it does not demonstrate the impact on prevalence, nor whether this is cost-effective. Assistance has been associated with a lower risk for technique failure or transplantation [24], but a higher risk for death as the patients were older and frailer. So it is possible that developing assisted PD services will increase PD prevalence, but mortality rates are likely to be high given the older, frailer population. Increasing self-care PD use in the UK from the actual incident rates to 40–50% would be significantly cost-effective [18], but whether the added cost of assisted PD would reduce the cost advantages over HD is not clear. A study in the Netherlands demonstrated that assisted PD in elderly patients is a cost-effective option [35]. Such a study will be needed in the UK to confirm these results.

Our findings appear to be robust in that numerous secondary analyses were performed: assessing the influence of the definition of PD initiation (>1 or 90 days of treatment), assessing the effect of assisted PD by inclusion as a time-varying explanatory variable or by changing the definition of the outcome, assessing the impact of competing events and adjusting for the effect of RRT start year as a linear effect, an FP or as a

Table 5. Adjusted cs-HRs (Cox model) and sd-HR (Fine and Gray model) for each event

Explanatory variable	PD		Transplant		Death	
	cs-HR (95% CI)	sd-HR (95% CI)	cs-HR (95% CI)	sd-HR (95% CI)	cs-HR (95% CI)	sd-HR (95% CI)
RRT starting time (linear, for a 1-year increase)	0.95 (0.93–0.98)***	0.95 (0.94–0.97)***	1.07 (1.02–1.12)**	1.03 (0.99–1.07)	1.03 (1–1.07)	0.98 (0.95–1)
Age (for a 10-year increase)	0.85 (0.80–0.90)***	0.88 (0.83–0.92)***	0.48 (0.43–0.54)***	0.53 (0.49–0.58)***	1.60 (1.44–1.77)***	1.89 (1.72–2.08)***
Gender						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	0.99 (0.81–1.21)	1 (0.84–1.19)	1.46 (1–2.10)	0.62 (0.43–0.89)*	1.02 (0.81–1.27)	1.16 (0.93–1.45)
Ethnicity						
White	Reference	Reference	Reference	Reference	Reference	Reference
Non-white	1 (0.69–1.48)	1 (0.72–1.39)	1.08 (0.62–1.86)	1.16 (0.69–1.95)	0.85 (0.49–1.46)	0.74 (0.44–1.26)
Primary renal disease						
Diabetes	Reference	Reference	Reference	Reference	Reference	Reference
Glomerulonephritis	0.84 (0.61–1.15)	0.87 (0.67–1.13)	1.15 (0.67–1.99)	1.47 (0.85–2.55)	0.52 (0.35–0.77)***	0.59 (0.41–0.85)**
Renal vascular disease	0.94 (0.68–1.29)	0.96 (0.73–1.27)	0.79 (0.37–1.66)	0.85 (0.40–1.79)	0.72 (0.53–0.99)*	0.71 (0.53–0.96)*
Polycystic	1 (0.68–1.47)	1 (0.72–1.39)	2.94 (1.68–5.13)***	3.65 (2.15–6.20)***	0.26 (0.11–0.58)**	0.22 (0.10–0.50)***
Pyelonephritis	1.08 (0.72–1.60)	1.04 (0.75–1.44)	1.16 (0.53–2.54)	1 (0.42–2.39)	0.71 (0.44–1.14)	0.70 (0.44–1.12)
Uncertain aetiology	1.16 (0.84–1.62)	1.16 (0.87–1.53)	1.30 (0.67–2.53)	1.32 (0.68–2.55)	0.92 (0.62–1.37)	0.61 (0.41–0.88)*
Other	0.60 (0.42–0.86)**	0.63 (0.46–0.87)**	1.17 (0.66–2.08)	1.32 (0.75–2.29)	1.07 (0.77–1.48)	1.30 (0.92–1.82)

*P<0.05, **P<0.01, ***P<0.001.

categorical variable. We also studied a sufficient time period to establish underlying trends, allowing a clearer assessment of the impact of introducing assisted PD. The finding that transplantation did not explain this fall in PD usage over time requires replication in a national cohort. The assisted PD observational study, and in particular, the estimated effect size service had the greatest impact on older, presumably frailer, patients, providing the benefits of home dialysis to a population that would otherwise miss out.

Our study has limitations. We cannot prove causality in an requires replication in a national cohort. The assisted PD observational study, and in particular, the estimated effect size service had the greatest impact on older, presumably frailer, relies on the assumption that patients who only perform patients, providing the benefits of home dialysis to a assisted PD would not otherwise start PD, although our population that would other-wise miss out.

experiences that most patients who might have been able to perform PD independently do progress to full independence, which would minimize this bias. Our study is further limited by its single centre, retrospective design and clearly needs repeating in a prospective, multicentre cohort, such as a national registry. Further evaluation with a randomized controlled trial, while desirable from the perspective of gaining high-quality evidence, would be challenging. A cluster design would be required, with ethical concerns regarding withdrawing existing services from centres randomized to the control arm. Healthcare systems that currently do not provide assisted PD offer the opportunity to study its introduction using a step-wedge design, including a health economic analysis.

We do not have data on comorbidity for patients who did not have PD, although comorbidity is correlated with primary renal disease so is partially adjusted for. As with most studies, there was limited missing data, but multiple imputation is a robust strategy to minimize the bias and loss of power this can introduce. Due to difficulties in competing risks models of pooled imputed datasets, complete case analysis was used resulting in slightly wider CIs. Our usage of assisted PD might differ from other centres, reflecting a flexible approach to the use of assisted PD not confined to new starters only but responding to the changing needs of the patient, which could limit the generalizability of our results. However, the variability in usage of assisted PD in different units is poorly understood, and we are planning a study to characterize this. There were insufficient events to consider technique failure.

In conclusion, this study shows that, in our centre, introducing an assisted PD service that was monitored and sustained led

SUPPLEMENTARY DATA

Supplementary data are available at [ndt online](https://academic.oup.com/ndt/advance-article-abstract/doi/10.1093/ndt/gfz287/5809186).

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CONFLICT OF INTEREST STATEMENT

The results of this article have not been published before, except in abstract format. M.L. reports speakers' honoraria and travel sponsorships from Baxter Healthcare and Fresenius Medical Care, as well as a consultancy fee from NxStage Medical and a research grant from Baxter Healthcare. S.J.D. reports speakers' honoraria from Fresenius Medical Care and Zytotec, and a research grant from Baxter Healthcare. No other co-authors report any potential conflicts of interest. The items documented here were in no way related to any part of the research or results contained or presented in this manuscript, although they may be perceived to be.

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IV. Trends in assisted peritoneal dialysis usage over the last decade

1. Introduction

France has one of the longest experiences with assisted PD programs (69,70). According to the RDPLF, a majority of incident patients treated by PD from 1995 to 2006 were considered unable to perform self-care PD and needed assistance. The assistance was mainly provided by a private nurse (45%), and to a lesser extent by a family member (7%) (74). With the population in ESKD growing older and frailer, an increase in assisted PD usage could be anticipated. However, because of the aging population and isolation of the elderly, one could suppose that the possibility of relying on family members for the assistance of PD patients could have decreased over time.

Strategic incentives to increase home dialysis by altering remuneration for these therapies are being introduced (115). To encourage PD in older patients in France, nurse-assisted PD in nursing homes became fully covered by healthcare insurance in 2011 (116). The impact of this incentive remains however unknown, as well as the longitudinal trends in the use of assisted PD over time.

In this second part of the thesis, we firstly wanted to describe the trends in assisted PD utilization and the trends in the type of assistance provided to PD patients over the past decade in France. Secondly, we ought to estimate whether the coverage of nurse-assisted PD in nursing home implemented at the national level in 2011 was associated with an increase in the utilization of nurse-assisted PD.

2. Materials and methods

For this part of the analysis, data from the RDPLF was used. All adults over 18 years starting PD in France between 1 January 2006 and 31 December 2015 were included.

Information on the type of assistance provided and comorbidities were obtained from the registry.

In the complete cohort, the events of interest were assisted PD, nurse-assisted PD and family-assisted PD at dialysis initiation. Assisted PD was defined as PD performed at the patient's home with the help of a community nurse (nurse-assisted PD) or a family member or a partner (family-assisted PD). Both PD modality (Eg CAPD or APD) could be chosen by assisted PD patients, according to their preferences. We also wanted to evaluate the use of CAPD over time and the association between the type of assistance and PD modality (Eg CAPD and APD). A second cohort included assisted-PD patients only. In that part of the analysis, the event of interest was the use of CAPD at dialysis initiation.

Our main explanatory variable was the time, or PD start year, between 1 January 2006 and 31 December 2015. Its functional form was explored with regression splines, transformation of the variable to a linear or categorical variable was performed based on the aspect of the graph of the functional form of the predictor. For the secondary objective, the explanatory variable was the time period following the implementation of the coverage of nurse-assisted PD in nursing home (the number of years between 2011 and the year of PD start).

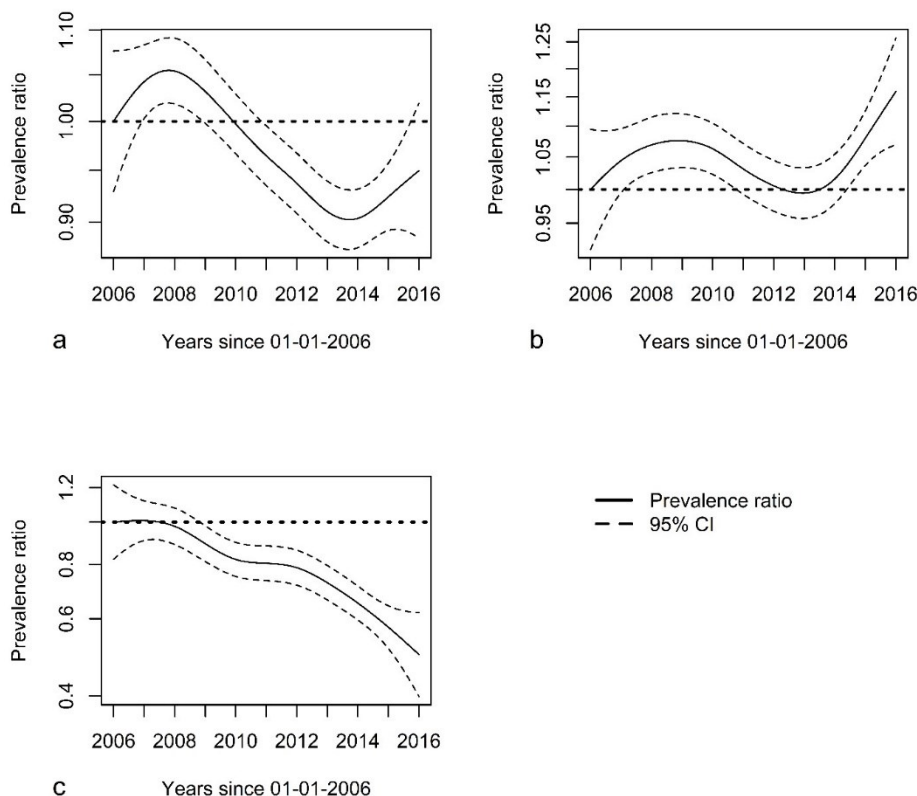
To explore the association between the time variable and the events of interest, prevalence ratios (PR) and their 95% CI were estimated using a Cox regression model with robust variance. As recommended, in the Cox model, a constant risk period equal to one was assigned to every patient in the cohort (103) (figure 8). To evaluate the association between the time variable and CAPD utilization, analyses were restricted to the cohort of patients on assisted PD and subsequently to the nurse-assisted PD and family-assisted PD subgroups.

Missing data were less than 5%, enabling us to use a complete case analysis.

3. Results

Of the 11987 incident patients on PD included in the study, 6149 (51%) were on assistance: 5052 (82%) were on nurse-assisted PD and 1097 (18%) were on family-assisted PD. In the adjusted analysis, calendar time was associated with the assisted PD rate: it declined from 2008 until 2013, before flattening out, and then it increased from 2014. Nurse-assisted PD increased significantly after 2012, whereas family-assisted PD linearly declined over the study period (figure 15).

Figure 15. Prevalence ratio of assisted PD initiation over time



Change in the PR of assisted PD initiation over time. Solid lines represent the rates of receiving assisted PD at any point during follow-up, by the year PD was initiated, when compared with 2006, expressed as PR. The analysis was adjusted for age, gender, ethnicity and underlying nephropathy using a Cox regression model with robust variance (95% CI shown by dashed lines). The assisted PD PR over the study period was not linear. The PR for assisted PD was defined as PD performed at the patient's home with the help of a community nurse or family member (a), for nurse-assisted PD only (b) and family-assisted PD only (c).

The relative use of CAPD increased over the study period, notably between 2012 and 2015. This increase was noted in both nurse and family-assisted PD.

4. Discussion

With the ESKD population growing older and frailer, an increase over the years in the use of assisted PD could be expected. However, our results highlight a different pattern: we observed a decline in the rate of assisted PD until 2013, while the total number of dialysed patients continued to increase (4). The decline in the assisted PD rate was mainly the consequence of a linear decline in family-assisted PD utilization.

The linear decline observed in family-assisted PD utilization could be explained by several factors. There was a modification in the state of health of caregivers over the study period, with caregivers suffering more and more from chronicle diseases (117–120). Secondly, social deprivation in the elderly has been increasing steadily (121). Finally, the proportion of frail and dependent patients did not decrease over time, which could influence the caregiver's burden (28,122–125).

The uptake in nurse-assisted PD observed from 2013 could reflect the effect of an economic incentive implemented in November 2011, fully covering the fees generated by nurse assistance even if the patients reside in a nursing home (116,126). Before 2011, most nursing home were not necessarily willing to pay for the additional charges generated by nurse assistance. Thus, most ESKD patients on PD did not have access to nursing homes or had to change modality to HD to be accepted. We believe that this economic incentive translated into an increase in nurse-assisted PD utilisation.

The use of CAPD increased over the study period. As technique survival, peritonitis-free survival and quality of life are similar between CAPD and APD in assisted PD patients (127,128), both modalities should be offered to assisted PD patients.

Our study shows that, due to a decline in family assistance, assisted PD currently relies mainly on nurse assistance. These findings, in light with our previous results highlighting the positive impact of assisted PD services on PD initiation, emphasize the importance of further promoting nurse assistance, eventually through economic incentives (129).

5. Article



ORIGINAL ARTICLE

Trends in assisted peritoneal dialysis over the last decade: a cohort study from the French Peritoneal Dialysis Registry

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ABSTRACT

Background. There is limited information available on the use of assisted peritoneal dialysis (PD) over time and the impact of economic incentives on its utilization. The aim of this study was to describe the trends in assisted PD utilization and the type of assistance provided. We wanted to estimate if an economic incentive implemented in 2011 in France was associated with an increase in the utilization of nurse-assisted PD.

Methods. This retrospective, multicentre study, based on data from the French Language Peritoneal Dialysis Registry, analysed 11 987 patients who initiated PD in France between 1 January 2006 and 31 December 2015. Adjusted Cox regression with robust variance was used to examine the initiation of assisted PD, both nurse-assisted and family-assisted, accounting for the nonlinear impact of the PD starting time.

Results. There were 6149 (51%) incident patients on assisted PD, 5052 (82%) on nurse-assisted PD and 1097 (18%) on family-assisted PD over the study period. In the adjusted analysis, calendar time was associated with the assisted PD rate: it declined from 2008 until 2013 before flattening out and then it increased after 2014. Nurse-assisted PD utilization increased significantly after 2012, whereas family-assisted PD utilization decreased linearly over time (prevalence ratio ¼ 0.94, 95% confidence interval 0.92–0.97).

Conclusions. The assisted PD rate decreased until 2013, mainly because of a decline in family-assisted PD. The uptake in nurse-assisted PD observed from 2013 reflects the effect of an economic incentive adopted in late 2011 to increase PD utilization.

Keywords: assisted peritoneal dialysis, chronic kidney disease, economic incentives, longitudinal trends, peritoneal dialysis

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INTRODUCTION

The initiation of dialysis can be emotionally challenging for patients and families; presenting patients with choices of dialysis modality may ease the burden of stress and anxiety. Older age, comorbidities, physical disabilities and psychosocial problems act as barriers to home dialysis [1–5].

Compared with in-centre haemodialysis (HD), peritoneal dialysis (PD) offers several advantages, such as the avoidance of transport to and from the dialysis unit, avoidance of difficulties in creating vascular access and haemodynamic instability during the HD session [3, 6–8]. By overcoming some of the conditions that act as a barrier to self-care PD [4, 9], assistance can improve the accessibility of home dialysis and thus favour quality of life in elderly patients [3, 9–11].

Home assistance programmes have been implemented in several countries in recent decades. Depending on the country, the assistance can be provided by a healthcare technician, a community nurse, and a trained family member or partner [12].

With the first programmes being implemented in the 1980s, France has one of the longest experiences of assisted PD [13, 14]. Nurse-assisted PD is fully covered by the French healthcare insurance. Notably, assisted PD remains cheaper than in-centre HD, even after the additional costs for nurse assistance [15]. Assisted PD allows patients to choose their PD modality [e.g. automatic peritoneal dialysis (APD) or continuous ambulatory PD (CAPD)] and the type of assistance (nurse or a family-assisted PD). According to the French Language Peritoneal Dialysis

Registry (RDPLF), >50% of incident patients treated by PD from 1995 to 2006 were considered unable to perform self-care PD and needed assistance. The assistance was mainly provided by a private nurse (45%) and to a lesser extent by a family member (7%). In the elderly population, >80% needed assistance [16].

Strategic economic incentives to increase home dialysis by altering remuneration for these therapies are being introduced [17]. Despite these incentives and the many advantages home dialysis can offer, PD use has been declining in recent decades [18], while the total number of dialysis patients has increased [19, 20]. It is unclear whether this decline is linked to an ageing population, which may be associated with limited use of home therapy unless assistance is provided. With the population in CKD growing older and frailer, we could anticipate an increase in assisted PD use. One may also argue that the possibility of re-lying on family members for the assistance of PD patients could have decreased over time. To encourage PD in older patients in France, nurse-assisted PD in nursing homes became covered by healthcare insurance in 2011 [21]. To our knowledge, there are no data in the literature describing the longitudinal trends in the use of assisted PD.

The aim of this study was to describe the trends in assisted PD utilization, the trends in the type of assistance provided to PD patients and the PD modalities used for the assisted PD patients over the past decade in France. The secondary objective was to estimate whether the coverage of nurse-assisted PD in nursing home implemented at the national level in 2011 was associated with an increase in the utilization of nurse-assisted PD.

MATERIALS AND METHODS

Study population

This was a retrospective study using data from the RDPLF. All adults >18 years starting PD in France between 1 January 2006 and 31 December 2015 were included. No patient was lost to

follow-up. The RDPLF database has been shown to be reliable, with coverage of 99% in France in 2016 [22, 23].

Age at PD start, gender, underlying nephropathy, diabetes mellitus, previous therapy before PD initiation (HD or renal transplantation), suboptimal starters (defined as a period of <30 days on HD before PD initiation) and centre category (academic, community, non-profit and private) were obtained from the registry [24]. To evaluate patient comorbidities, the Charlson comorbidity index (CCI) was extracted from the database, and the modified CCI was calculated by subtracting the age subscore. For centre size estimation, we calculated the number of incident PD patients per centre per year of participation during the study period [25].

Events of interest

In the complete cohort, the events of interest were assisted PD, nurse-assisted PD and family-assisted PD at dialysis initiation. Assisted PD was defined as PD performed at the patient's home with the help of a community nurse (nurse-assisted PD) or a family member or a partner (family-assisted PD).

We also wanted to evaluate the use of CAPD over time and the association between type of assistance and PD modality (CAPD/APD). A second cohort included nurse- and family-assisted patients. In that part of the analysis, the event of interest was the use of CAPD at dialysis initiation.

To provide additional information, we have also estimated the occurrence of PD failure, caused by death or transfer to HD, and renal transplantation during the study period. The time from PD start to the first episode of peritonitis was also calculated. Both technique survival and peritonitis rates were evaluated in the complete cohort and in the nurse- and family-assisted cohort.

Explanatory variable

The main explanatory variable was the time, or PD start year, between 1 January 2006 and 31 December 2015. For the secondary objective, the explanatory variable was the time period following the implementation of the coverage of nurse-assisted PD in nursing home (the number of years between 2011 and the year of PD start).

Statistical analysis

Continuous variables were described by the median (first and third quartile), and categorical variables were described by frequencies and percentages. Regression splines were used to explore the functional form of the length of time from the inclusion date until the end of the inclusion period. Transformation of the continuous time variable to a categorical variable was performed based on the aspect of the graph of the functional form of the predictor.

When the proportion of the event of interest is >10%, the odds ratio (OR) overestimates the prevalence ratio (PR). Alternative methods have been described in the literature for the analysis of binary outcomes in longitudinal studies, including using the PR instead of the OR. The Cox model with robust variance is valid for estimating the PR [26].

To explore the association between the time variable and the events of interest in the complete cohort, PRs and 95% confidence intervals (CIs) were calculated using a Cox regression model with robust variance. As recommended, in the Cox model, a constant risk period equal to one was assigned to every patient in the cohort [26].

To evaluate the association between the time variable and CAPD utilization, analyses were restricted to the cohort of patients on assisted PD and subsequently to the nurse-assisted PD and family-assisted PD subgroups.

Cumulative incidence curves were drawn for each possible PD outcome (death, transfer to HD and renal transplantation) and for peritonitis events. Technique survival and peritonitis rates according to the type of assistance were compared using the Logrank test. Conditional probabilities for the event of interest were estimated at specific time points.

A bivariable analysis was performed to estimate the association between each variable and the event of interest. The time variable was included *a priori* in the multivariate analysis; otherwise, variables were included in the model based on the results of the change in the estimate procedure with a cut-off value of 10%. Interactions between time and the other covariates were tested in the multivariate models.

Missing data were <5%, enabling us to use a complete case analysis. Analyses were performed with R 3.4.3 (R Foundation for Statistical Computing, Vienna Austria, including the survival package).

RESULTS

Patient characteristics

Of the 11 987 incident patients on PD included in the study, 6149 (51%) patients were on assisted PD: 5052 (82%) were on nurse-assisted PD and 1097 (18%) were on family-assisted PD. The number of patients starting PD per year is displayed in Figure 1. The median [interquartile range (IQR)] time on PD was

19.3 months (8.4–34.5 months). Compared with self-care PD patients, those on assisted PD were older, more frequently diabetic and had more comorbidities. Patient characteristics according to the type of assistance are described in Table 1. Incident patients' age and CCI by year of PD start are described in Table 2.

Association between calendar time and the rate of assisted PD utilization

In the multivariable analysis, time was associated with the assisted PD rate, whether included in the regression model as a regression spline (Figure 2) or as a categorical variable (Table 3).

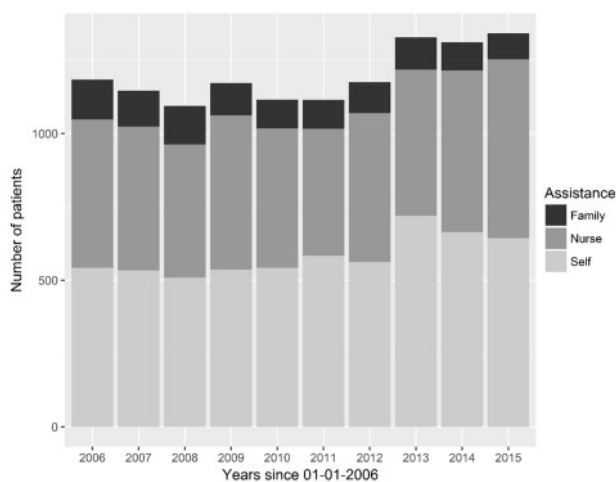


FIGURE 1: Number of patients starting PD per year over the study period.

The year 2013 was the time point with the lowest rate of assisted and nurse-assisted PD utilization and was chosen as the reference class in the corresponding modelling. There was a linear relationship between time and family-assisted PD utilization; thus, the PD start year was defined as a linear variable in this model.

Compared with 2013, starting PD in 2006, 2007, 2008, 2009, 2010, 2012 or 2015 was strongly associated with the utilization of assisted PD. Nurse-assisted PD utilization increased significantly after 2012, whereas family-assisted PD utilization decreased linearly over time (PR ¼ 0.94, 95% CI 0.92–0.97; Table 3).

Age, gender, diabetes, modified CCI, a suboptimal start, underlying nephropathy, renal replacement therapy before PD initiation and centre experience were associated with assisted PD (Table 3). There were no significant interactions between PD start year and the other covariates.

Association between calendar time and the rate of CAPD utilization in the assisted PD, nurse-assisted PD and family-assisted PD subgroups

Based on the shape of the regression spline, the PD start year for this part of the analysis was transformed into a categorical variable composed of three classes: 2006–10, 2010–12 (reference class) and 2012–15. In the unadjusted and adjusted analyses, the PD start year was associated with an increased rate of CAPD utilization, whether included in the Cox regression model as a regression spline (data not shown) or as a categorical explanatory variable (Table 4).

Starting PD in 2012, 2013, 2014 or 2015 was strongly associated with an increased rate of CAPD utilization (PR ¼ 1.16, 95% CI 1.08–1.23). The PR change over time followed a similar pattern in nurse-assisted PD patients (PR ¼ 1.13, 95% CI 1.05–1.21)

and family-assisted PD patients (PR ¼ 1.24, 95% CI 1.03–1.49; Table 4).

Age, gender, modified CCI, a suboptimal start, therapy before PD initiation and centre experience were associated with CAPD initiation (Table 4). There were no significant interactions between PD start year and the other covariates.

Technique survival and peritonitis rates according to the type of assistance

The median (IQR) PD duration for the complete cohort was 16.9 months (7.38–30.9). There were 10 942 (91%) PD failures during the study period, including 4252 (35%) deaths and 3648 (30%) transfers to HD. Furthermore, 2262 (19%) patients had a renal transplantation. According to the type of assistance, the median (IQR) PD duration was 16.6 months (6.1–31.5) and 15.5 months (7.1–31.3) for patients on nurse- and family-assistance, respectively.

Technique survival rates did not differ according to the type of assistance (P ¼ 0.57). Conditional probabilities using the cumulative incidence method for the events are provided in Table 5.

In the complete cohort, there were 4421 (37%) episodes of peritonitis, with a median (IQR) time to peritonitis of 8.9 months (3.1–19.6). There were 1826 (36%) episodes of peritonitis in the nurse-assistance group and 406 (37%) in the family-assistance group. Median (IQR) time to peritonitis were of 8.8 months (2.8–19.8) and 8.5 months (2.2–20.3), respectively. Patients on nurse assistance tended to have less peritonitis compared with patients on family assistance even though the results were not

significant (P ¼ 0.08). The cumulative incidence of peritonitis at

Table 1. Patients characteristics according to the type of assistance (N 5 11 987)

Variables	All patients (n ¼ 11 987)	Nurse-assisted (n ¼ 5052)	Family-assisted (n ¼ 1097)	Self-care (n ¼ 5838)
Age at PD initiation, median (IQR) ^a	69.2 (54.7 – 80.1)	79.6 (72.3 – 84.6)	74.3 (65 – 81.7)	56.5 (43.9 – 67.1)
Gender (male), n (%)	7101 (59)	2686 (53)	674 (62)	3741 (64)
Diabetes, n (%)	4026 (34)	2204 (44)	529 (48)	1293 (22)
Modified CCI, median (IQR)	3 (2 – 5)	4 (3 – 6)	5 (3 – 6)	3 (2 – 4)
Underlying nephropathy, n (%)				
Diabetic	2372 (20)	1247 (25)	312 (29)	813 (14)
Interstitial nephritis	784 (7)	276 (6)	64 (6)	444 (8)
Glomerulonephritis	1827 (15)	283 (6)	91 (8)	1453 (25)
Polycystic kidney disease	800 (7)	109 (2)	29 (3)	662 (11)
Unknown	1359 (11)	625 (12)	115 (10)	619 (11)
Uropathy	525 (4)	112 (2)	32 (3)	381 (6)
Vascular	3828 (32)	2256 (45)	412 (38)	1160 (20)
Systemic disease	333 (3)	83 (1)	22 (2)	228 (4)
Other	105 (1)	41 (1)	12 (1)	52 (1)
Missing	54	20	8	26
Suboptimal starters, n (%)	1131 (9)	558 (11)	105 (10)	468 (8)
Treatment before PD, n (%)				
No therapy	9486 (79)	4188 (83)	860 (78)	4438 (76)
HD	2072 (17)	815 (16)	222 (20)	1035 (18)
Renal transplantation	406 (4)	40 (1)	15 (2)	351 (6)
Missing	23	9	0	14
First PD modality (CAPD), n (%)	8971 (75)	4357 (86)	801 (73)	3813 (65)
Type of centre, n (%)				
Community hospital	5763 (48)	2562 (51)	528 (48)	2673 (46)
Academic hospital	2326 (20)	893 (18)	204 (19)	1229 (21)
Non-profit	2863 (24)	1107 (22)	268 (24)	1488 (25)
Private hospital	1035 (8)	490 (9)	97 (9)	448 (8)
Centre experience, n (%) (new patients per year)				
≤10	4746 (40)	1964 (39)	437 (40)	2345 (40)
>10	7241 (60)	3088 (61)	660 (60)	3493 (60)

^aIn years.

Table 2. Age and CCI of the incident patients, by year of PD start

PD start year	Age [median (IQR)]	CCI [median (IQR)]	CCI ≥7 [n (%)]
2006	71.5 (55 – 80.4)	4 (2 – 5)	96 (8)
2007	69.4 (55.9 – 79.7)	3 (2 – 5)	108 (9)
2008	68.8 (53.6 – 78.9)	3 (2 – 5)	109 (10)
2009	70.3 (54.8 – 80.9)	4 (2 – 5)	110 (9)
2010	69.8 (54.6–80.2)	4 (2–5)	108 (10)
2011	67.2 (53–80.2)	3 (2–5)	105 (9)
2012	70 (54.6–80)	3 (2–5)	110 (9)
2013	67.2 (53.9–80.1)	3 (2–5)	129 (10)
2014	68.4 (55.6–80.2)	3 (2–5)	136 (10)
2015	69.9 (56.2–80.7)	4 (2–5)	152 (11)

2 years was of 50.5, 49.4 and 52.1% for the complete cohort, nurse-assistance and family-assistance groups, respectively.

DISCUSSION

Assisted PD programmes are available in different countries around the world, with differences from one country to another [12]. To our knowledge, the trend in the utilization of assisted PD among incident PD patients over time has not yet been documented at a national level. We hereby provide a description of

the utilization of assisted PD over a decade in a country where assisted PD has been available for >30 years and is fully covered by healthcare insurance. The high exhaustivity of the RDPLF makes it a reliable database [22, 23].

With the CKD population growing older and frailer, it would be anticipated that the use of assisted PD should increase over the years. However, our results show a different pattern; there was a decline in the rate of assisted PD until 2013, while the total number of dialysed patients continued to increase [19]. The decline in the assisted PD rate was mainly attributed to a linear decline in family-assisted PD utilization.

In contrast, after 2013, there was an increased utilization of nurse-assisted PD over time (Figure 2). Surprisingly, patients' age and comorbidities remained stable during the study period (Table 2), leading to the hypothesis that the potential rate of patients who needed assistance did not decrease during the decade.

The linear decline observed in family-assisted PD utilization could be explained by several factors. First, there was a modification in the state of health of caregivers. In a French survey published in 2008, 48% of the caregivers were suffering from chronic disease, and 29% declared that they were suffering from anxiety and stress [27]. Life expectancy has been rising in France over the past decade; however, while life expectancy without disability remains stable (64.5 years old for women and 63.4 years old for men) [28], the number of people suffering from

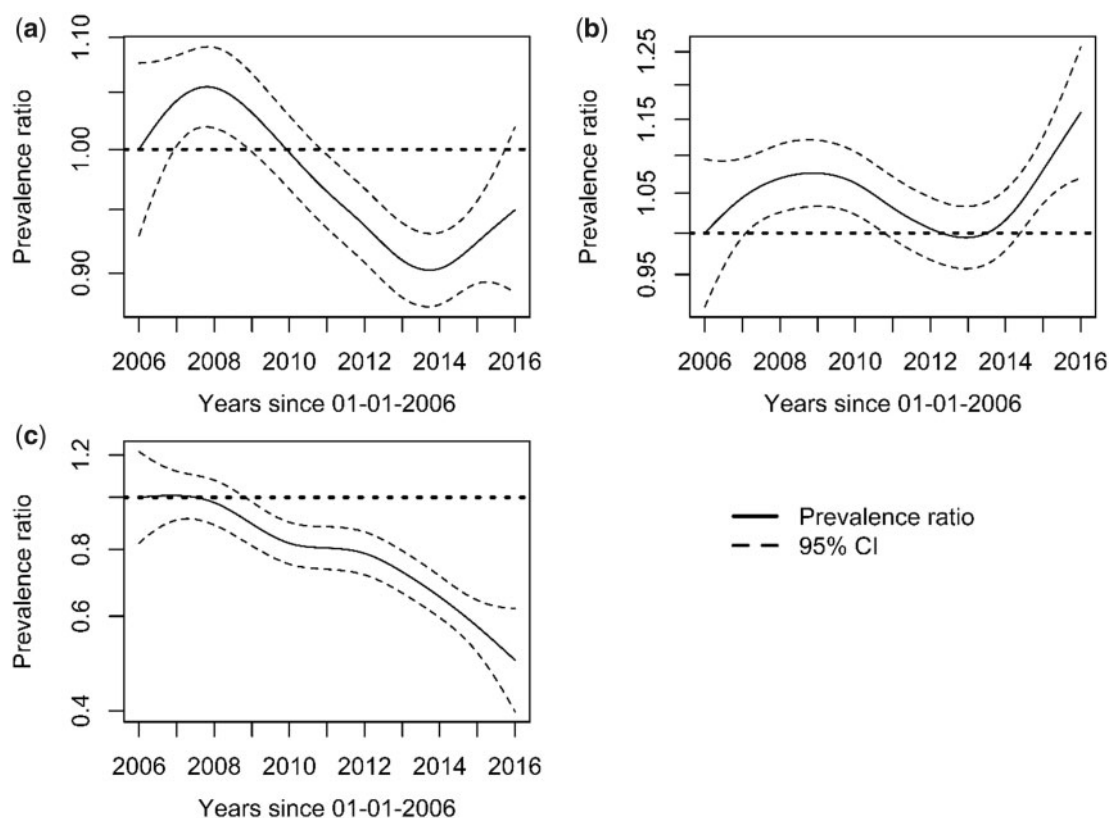


FIGURE 2: PR of assisted PD initiation over time. Change in the PR of assisted PD initiation over time. Solid lines represent the rates of receiving assisted PD at any point during follow-up, by the year PD was initiated, when compared with 2006 (expressed as a PR). The analysis was adjusted for age, gender, ethnicity and underlying nephropathy using a Cox regression model with robust variance (95% CI shown by dashed lines). The assisted PD PR over the study period was not linear. The PR for assisted PD was defined as PD performed at the patient's home with the help of a community nurse or a family member (a), for nurse-assisted PD only (b) and family-assisted PD only (c).

chronic disease has been constantly rising [29, 30]. The number of caregivers in France is estimated to be 11 million, of which almost 35% are aged >60 years old, and 74% feel that being a caregiver has an impact on their own health [31, 32]. Secondly, social deprivation in the elderly (>75 years old) has been increasing steadily; in 2014, 27% of elderly individuals were considered to live with social deprivation compared with 16% in 2010. The population with social deprivation is now composed of more than a quarter of the people aged >75 years. This increase has been associated with a combination of several factors: an increase in the proportion of elderly people with disabilities, a relative decline in associative practices and a loosening in family relationships [33].

Finally, the proportion of patients on PD with a CCI >7 did not decrease over time (Table 2), reflecting frailty and dependency, which could influence the caregiver's burden. The increase in caregiver burden, often associated with a reduction in psychological health, has been previously reported [34, 35]. It has recently been shown that a high proportion of patients will observe a decline in functional status in the first 6 months after initiating dialysis. In this study, the percentage of caregivers reporting a high burden of care increased from 23 to 38% after dialysis initiation [36]. In a study from our team, compared with autonomous PD patients, patients with nurse assistance had a lower risk of transfer to HD, while those with family assistance had a similar risk of transfer to HD. This finding could be partly explained by the usefulness of nurse assistance to reduce the burden of PD for both patients and their families [11, 37, 38]. As

the caregiver burden increased over time, family assistance declined. Interventions will be needed in the future to remove this burden and facilitate the task of caregivers.

On the other hand, the recent uptake in nurse-assisted PD could be explained by economic incentives and/or better coverage of home dialysis.

Economic incentives to increase home dialysis by altering remuneration for these therapies are being introduced in some countries. A recent workshop concluded that economic incentives were effective at increasing the use of home dialysis [17]. However, the time until an impact on incident home dialysis numbers can be observed remains unclear.

In France, nursing homes receive a financial budget from the healthcare insurance that covers collective medical costs (human resources and medical devices). The nursing time dedicated to each patient is based on a standard medical care evaluation. However, patients on PD might need assistance up to four times a day, 7 days a week, increasing the need for human resources. Nurse-assisted PD is fully covered by the healthcare insurance in France; however, prior to 2011, no fee was paid if the patient resided in a nursing home [39]. According to Dratwa *et al.*, the evaluated additional costs generated by nurse-assistance were ~23 400 e/patient/year for CAPD (four exchanges per day) and 18 200 e/patient/year for APD [39]. Most nursing homes were not willing to pay for these additional charges. As a consequence, most end-stage renal disease patients on PD did not have access to nursing homes or had to change modality to HD to be accepted. Thanks to an economic

Table 3. Association between PD start year and the PR of assisted PD initiation, adjusting for patient characteristics, for each type of assistance

All assistance		Nurse-assistance	Family-assistance
Explanatory variable	PR (95% CI)	PR (95% CI)	PR (95% CI)
PD start year (reference ¼2013)			PD start year ^a
2006	1.17 (1.07–1.29)	1.08 (0.96–1.22)	0.94 (0.92–0.97) ^a
2007	1.27 (1.15–1.39)	1.19 (1.05–1.34)	
2008	1.24 (1.12–1.37)	1.13 (0.99–1.27)	
2009	1.21 (1.10–1.32)	1.18 (1.05–1.33)	
2010	1.14 (1.04–1.26)	1.14 (1.02–1.28)	
2011	1.09 (0.99–1.21)	1.08 (0.96–1.21)	
2012	1.16 (1.06–1.28)	1.15 (1.03–1.27)	
2013	Reference	Reference	
2014	1.08 (0.99–1.19)	1.14 (1.02–1.29)	
2015	1.12 (1.03–1.23)	1.24 (1.11–1.34)	
Age, for a 10-year increase	1.79 (1.75–1.83)	1.83 (1.79–1.88)	1.19 (1.14–1.25)
Gender, male	0.71 (0.68–0.74)	0.70 (0.66–0.73)	1.06 (0.94–1.20)
Diabetes	1.13 (1.07–1.20)	1.10 (1.03–1.18)	1.21 (1.02–1.44)
Modified CCI (per unit)	1.09 (1.08–1.11)	1.06 (1.05–1.08)	1.14 (1.10–1.18)
Suboptimal starters	1.11 (1.04–1.19)	1.17 (1.07–1.26)	0.90 (0.73–1.10)
Underlying nephropathy			
Polycystic kidney disease	Reference	Reference	Reference
Diabetes	2.30 (1.93–2.74)	2.16 (1.77–2.63)	1.93 (1.26–2.96)
Interstitial nephritis	2.16 (1.79–2.61)	2.04 (1.65–2.51)	2.02 (1.28–3.18)
Glomerulonephritis	1.36 (1.13–1.63)	1.26 (1.02–1.55)	1.42 (0.92–2.18)
Unknown	2.18 (1.83–2.59)	2.09 (1.72–2.54)	1.73 (1.13–2.66)
Uropathy	1.84 (1.48–2.29)	1.72 (1.34–2.21)	1.79 (1.06–2.99)
Vascular	2.35 (1.99–2.78)	2.22 (1.84–2.68)	1.91 (1.27–2.87)
Systemic disease	1.87 (1.47–2.38)	1.77 (1.35–2.33)	1.72 (0.97–3.04)
Other	2.23 (1.68–2.95)	2.06 (1.50–2.82)	2.43 (1.18–5.01)
Therapy before PD initiation			
No therapy	Reference	Reference	Reference
HD	1.14 (1.08–1.20)	1.04 (0.97–1.12)	1.32 (1.13–1.54)
Transplantation	0.54 (0.41–0.71)	0.54 (0.39–0.74)	0.67 (0.39–1.15)
Type of centre			
Academic hospital	Reference	Reference	Reference
Community hospital	1 (0.95–1.07)	1.03 (0.96–1.11)	0.94 (0.79–1.11)
Non-profit	1 (0.93–1.07)	0.98 (0.90–1.07)	1.08 (0.90–1.30)
Private hospital	0.94 (0.87–1.02)	0.94 (0.84–1.04)	0.99 (0.77–1.28)
Centre experience (new patients per year)			
≤10	Reference	Reference	Reference
>10	1.14 (1.09–1.20)	1.17 (1.10–1.23)	0.99 (0.87–1.13)

^aAccording to the spline regression, PD start year was modelled as a linear variable (per year).

incentive implemented in November 2011, the fees generated by nurse assistance are now fully covered, even if the patients reside in a nursing home [21]. That means that private nurses are paid, since 2011, to perform PD in the nursing home. We believe that this incentive translated into an increase in nurse-assisted PD from 2013. The funding models for dialysis can also impact the use of home dialysis. In the USA, the prospective payment system, a bundle payment, for the US Medicare End-Stage Renal Disease Programme was launched in January 2011. It reduced financial disincentives for facility use of home therapies. PD payment was set to be equivalent to in-centre HD treatment. The number of patients on PD increased by 15% between 2011 and 2013 [17, 40]. There was an increasing tendency of patients on PD to be treated in facilities with less PD experience, without any changes in mortality rates. This finding suggests a link between the funding model and the modality distribution [17, 40, 41].

As shown by the adjusted Cox model, the relative use of CAPD increased over the study period, notably between 2012

and 2015 (PR ¼ 1.16, 95% CI 1.08–1.23). This increase was noted in both nurse- (PR ¼ 1.13, 95% CI 1.05–1.21) and family-assisted PD (PR ¼ 1.24, 95% CI 1.03–1.49). In a recent study from our team, technique survival and peritonitis-free survival were similar between CAPD and APD in assisted PD patients [42]. In addition, a study of incident self-PD patients demonstrated a similar quality of life in both modalities, underlining the importance of the patient's choice [43]. Both modalities should be offered to assisted PD patients; however, in view of the CAPD rate, one may wonder if APD is considered by the PD team to be equally suitable as CAPD for assisted patients with physical disabilities or cognitive dysfunctions. Moreover, nursing homes are often reluctant to deal with cyclers during the night because of the small number of caregivers available at night in those facilities.

Older age, diabetes, a higher CCI and underlying nephropathy were also associated with an increased probability of assisted PD initiation, likely a reflection of increased comorbidity, frailty and dependency. Similar findings have been described previously [11, 25]. It has been demonstrated that functional

Table 4. Association between PD start year and the PR of CAPD initiation, adjusting for patient characteristics, for each type of assistance

Explanatory variable	All assistance	Nurse-assistance	Family-assistance
	PR (95% CI)	PR (95% CI)	PR (95% CI)
PD start year (category)	Reference	Reference	Reference
2010–12	Reference	Reference	Reference
2006–10	1.04 (0.97–1.11)	1.02 (0.94–1.09)	1.17 (0.98–1.41)
2012–15	1.16 (1.08–1.23)	1.13 (1.05–1.21)	1.24 (1.03–1.49)
Age, for a 10-year increase	1.20 (1.17–1.23)	1.17 (1.14–1.21)	1.21 (1.15–1.29)
Gender, male	0.95 (0.91–1.01)	0.96 (0.91–1.01)	0.98 (0.86–1.12)
Diabetes	0.99 (0.94–1.06)	1.02 (0.95–1.08)	0.90 (0.76–1.07)
Modified CCI (per unit)	1.02 (1.01–1.03)	1.02 (1.01–1.03)	1.02 (0.99–1.06)
Suboptimal starters	0.90 (0.83–0.97)	0.92 (0.84–0.99)	0.77 (0.59–0.99)
Underlying nephropathy			
Polycystic kidney disease	Reference	Reference	Reference
Diabetes	1.03 (0.86–1.24)	1.07 (0.87–1.32)	0.93 (0.60–1.46)
Interstitial nephritis	1.13 (0.93–1.38)	1.15 (0.93–1.44)	1.04 (0.64–1.70)
Glomerulonephritis	1.04 (0.85–1.27)	1.10 (0.88–1.37)	0.88 (0.55–1.42)
Unknown	1.07 (0.89–1.28)	1.14 (0.93–1.40)	0.78 (0.49–1.25)
Uropathy	1.21 (0.96–1.52)	1.27 (0.99–1.63)	1.11 (0.63–1.96)
Vascular Systemic disease	1.18 (0.99–1.40)	1.21 (1–1.46)	1.10 (0.72–1.68)
Other	0.94 (0.72–1.24)	1 (0.74–1.36)	0.72 (0.37–1.38)
Therapy before PD initiation			
No therapy	Reference	Reference	Reference
HD	0.86 (0.80–0.93)	0.86 (0.80–0.93)	0.91 (0.77–1.09)
Transplantation	0.71 (0.50–1.01)	0.63 (0.42–0.95)	1.01 (0.54–1.88)
Type of centre			
Academic hospital	Reference	Reference	Reference
Community hospital	0.84 (0.79–0.90)	0.79 (0.74–0.85)	1.01 (0.54–1.88)
Non-profit	0.99 (0.93–1.06)	0.92 (0.86–0.99)	1.37 (1.12–1.66)
Private hospital	0.94 (0.86–1.03)	0.87 (0.80–0.96)	1.31 (1.04–1.67)
Centre experience (new patients per year)			
≤10	Reference	Reference	Reference
>10	0.93 (0.88–0.97)	0.91 (0.87–0.96)	0.94 (0.82–1.08)

Table 5. Cumulative incidence of PD outcomes at specific times points with the cumulative incidence function estimate

Event per type of assistance	6 months	12 months	18 months	24 months
All patients				
Death	8.7	17.2	26.4	37.7
Transfer to HD	9	16.6	25.5	34.5
Renal transplantation	3.3	9.8	16.6	24.5
Nurse-assisted PD patients				
Death	15.9	30.2	45.9	64.2
Transfer to HD	8.7	13.9	20.3	26.4
Renal transplantation	0.5	1	1.8	2.6
Family-assisted PD patients				
Death	13.6	28.8	41.4	60.9
Transfer to HD	8.7	17.2	27.7	34.1
Renal transplantation	0.8	3.3	6.1	7.6

Results are expressed as percentages.

impairment is highly prevalent in older patients on assisted PD and is associated with comorbidities [44].

Technique survival and peritonitis rates in our population were similar to previous studies [11, 45]. Both types of assistance have been associated with a lower risk for technique failure or transplantation, but a higher risk for death as

the patients were older and frailer [11]. In older patients, nurse assistance has been associated with a lower risk for peritonitis [45]. Our findings are in line with previous studies, demonstrating the sustainability of assisted PD.

The use of PD remains low in France, with <10% of patients utilizing this modality [19]. Over time, patients starting dialysis seem to be older and more likely to be diabetic and have cardiovascular or respiratory comorbidities [19]. The use of assisted PD could reflect a nephrologist preference for this modality for older and frailer patients.

Our study has limitations; by nature, the observational design cannot lead to conclusions regarding causality. We have shown results on the use of assisted PD compared with all PD utilization; however, this study was not designed to show an effect on overall PD utilization as this would require data on all renal replacement therapy patients. Although the use of assistance can change over time, only the assistance at dialysis start was used for the analysis. Because of the particularity of the coverage in France, assisted PD utilization might differ from other countries, which could limit the generalizability of our results. However, we believe that the results of our study could help centres anticipate what could possibly happen in the future when implementing an assisted PD programme.

Our study also shows that, due to a decline in family assistance, assisted PD currently relies mainly on nurse assistance. It has been demonstrated that widespread adoption of assisted

PD services would significantly increase PD initiation [46]. Although there are added costs to nurse-assisted PD, a Netherlands study demonstrated that it is a cost-effective option [47] in elderly patients. To further develop PD utilization in developed countries, nurse assistance should be promoted. We believe that assisted PD programmes, notably nurse assistance, should be implemented in every PD centre to increase PD utilization [48]. Alternatively, economic incentives to the patient's family could be considered, to convince relatives to participate in PD care. Such incentives do not exist in France currently.

In conclusion, this study shows that in France, the assisted PD rate decreased until 2013, mainly because of the decline of family assistance. The uptake in nurse-assisted PD observed from 2013 probably reflects the effect of an economic incentive adopted in late 2011 to increase PD utilization for end-stage renal disease patients in nursing homes.

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CONFLICT OF INTEREST STATEMENT

None declared.

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V. Trends in peritoneal dialysis technique survival, death and transfer to haemodialysis

1. Introduction

One of the main limitations of PD relates to technique survival, which remains a major concern for ESKD patients and their nephrologists (82,83). Transfer to HD, mainly due to infection, inadequate dialysis and catheter dysfunction (82,130–135), is a barrier toward PD use and could partially explain the low PD prevalence (83).

When studying PD technique survival, the definition of the outcome of interest might change throughout studies. Lan et al, proposed to define technique survival by the composite end point of death or transfer to (HD) over 2 months (composite endpoint). To maximize the amount of information, transfer to HD (death-censored technique survival) and patient survival (transfer to HD censored) should be reported separately. Further, providing information regarding the cause of transfer to HD is critical if one wants to increase PD duration. The causes of transfer to HD could be classified as follows: infection, mechanical causes (catheter dysfunction), inadequate dialysis, social reasons, encapsulating peritoneal sclerosis, and other reasons (82).

There are both patient- and centre-level characteristics associated with transfer to HD (81,84,136,137). Notably, assisted PD has been associated with a lower risk of transfer to HD (114,127). Significant improvements have been observed in rates of peritonitis cure since 2010, which led to enhanced technique survival and decreased occurrence of transfer to HD over this period (84–87). Indeed, since 2010, PD cessation due to infection and death declined, whereas PD cessation due social reasons increased (85).

This part of the thesis aimed to estimate the longitudinal trends over time of technique survival (death and transfer to HD), transfer to HD (death censored), and patient survival (transfer to HD censored). This study was also carried out to estimate the evolution of the individual causes of transfer to HD over the past decade in France. Finally, we wanted to determine whether the calendar time effect on the events of interest was influenced by the assistance status (self-care PD, nurse-assisted PD, and family-assisted PD).

2. Materials and methods

Data from the RDPLF was used for this part of the analysis. All adults over 18 years starting PD in France between 1 January 2005 and 31 December 2016 were included. The end of the study period was June 20, 2019. Information on comorbidities and the type of assistance provided were obtained from the registry. Comorbidities and centres' characteristics were extracted from the registry. Time on PD was calculated in months between the date of PD initiation and the date of PD cessation (in case of transfer to HD, death or transplantation) or end of follow-up if none of these events had occurred.

The outcome of interest was PD cessation, studied by the occurrence of death on PD or transfer to HD over 2 months (composite end-point), death on PD (transfer to HD censored) and transfer to HD over 2 months (death censored), as illustrated in Figure 16. Among the patients transferred to HD, the event of interest was the cause of transfer (infection, inadequate dialysis, catheter issue, social issue, other causes linked with PD and other causes not linked with PD), studied one at a time. Of note, time to first event on PD (death or transfer to HD) was modeled. Death occurring on HD shortly after a transfer from PD was not analysed.

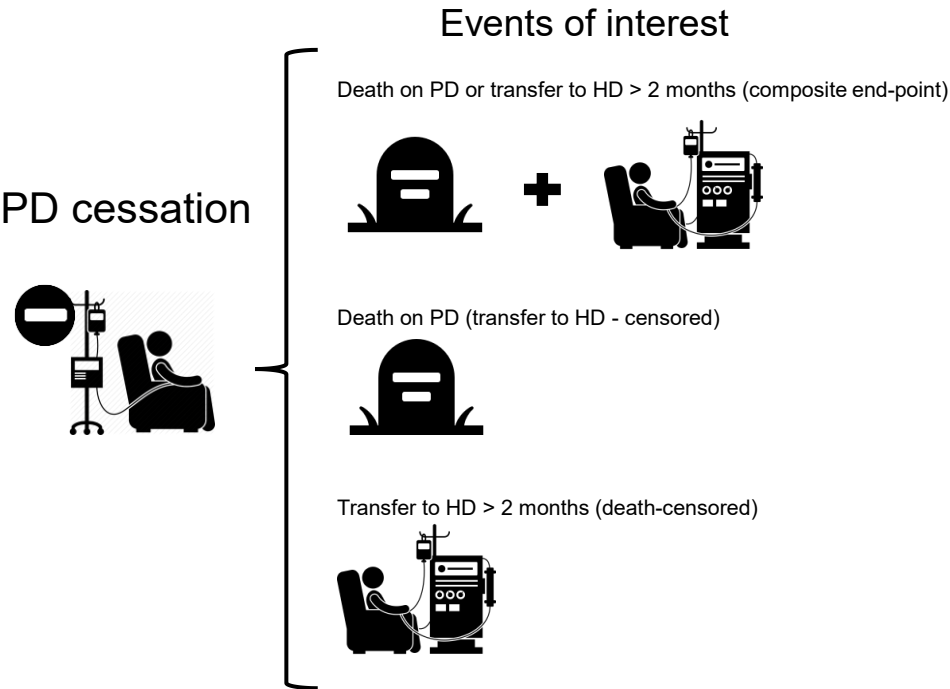
The main explanatory variable was calendar time, defined as the PD start year, between 1 January 2005 and 31 December 2016. Its functional form was explored with

regression splines, transformation of the variable to a linear or categorical variable was performed based on the aspect of the graph of the functional form of the predictor.

To explore the association between the time variable and the events of interest, PRs and their 95% CI were estimated using a Cox regression model with robust variance (103). In the complete cohort, the composite end point of death on PD or transfer to HD, death on PD (transfer to HD censored), and transfer to HD (death censored) were the events of interest. The analyses were performed in the self-care PD, nurse-assisted PD, and family-assisted PD subgroups separately. In the subset of patients transferred to HD, each cause of PD failure was an event of interest (one at a time). The analyses were also carried out in the self-PD, nurse-assisted PD, and family-assisted PD groups separately.

Less than 5% of the data on all variables were missing; we assumed the data to be missing at random, enabling us to use a complete case analysis.

Figure 16. Description of the events of interest



3. Results

Of the 14673 incident patients on PD included in the study, 10201 (69.5%) experienced PD cessation: 5495 (37.4%) died and 4706 (32.1%) were transferred to HD over the study period. The median time on PD was 19 months (interquartile range, 8-35 months). Causes of transfer to HD were mainly inadequate dialysis (1853 events, 39%) and infection (751, 16%).

In the adjusted analysis, calendar time was linearly associated with PD cessation due to death or transfer to HD and death (transfer to HD censored), which significantly decreased over time (PR 0.96, 95% CI 0.95-0.97 and PR 0.95, 95% CI: 0.94-0.96 respectively), regardless of the assistance status. Compared to 2009-2010, starting PD in 2005-2008 or 2011-2016 was strongly associated with a decreased rate of transfer to HD (PR 0.88, 95% CI: 0.81-0.96, and PR 0.91, 95% CI: 0.84-0.99 respectively).

Among the patients transferred to HD, the proportion of transfer for infections decreased over time (PR 0.96, 95% CI: 0.94-0.98), whereas it increased for other causes not linked to PD (PR 1.05, 95% CI: 1.03-1.08). The PR change over time followed a similar pattern in self-care PD patients, but not in nurse nor family-assisted PD patients.

Of note, transplantation rates remained stable over the study period.

4. Discussion

In this part of the thesis, we described the trends of PD cessation over a decade in a country where PD has been available for over 30. Our study shows that both PD cessation (due to either death or transfer to HD) and death (transfer to HD censored) declined linearly over time, without any differences whether patients were autonomous or assisted. The decline in transfers to HD rates, observed since 2011, is mainly the result of a significant decline in infection-related transfers, particularly in self-PD patients. No temporal trends of the impact

of assistance on patient and technique survival were observed in our study; this impact remained stable over time.

Our findings are in line with previous research (59,85,86,132,138). There is evidence that the peritonitis risk has decreased over time (132,139,140); when parallel, the rates of peritonitis cure improved (84). The enhancement of trainings and educational programs over the past decade may partly explain this finding, as educational programs, retraining and the systematic usage of hydroalcoholic solution for hand hygiene have been associated with a lower peritonitis rate (127,141–147). In addition, both centre size (86,114,133,134,148–151) and experience (81,138) impact PD outcomes, patients initiating PD in higher volume centres having a lower risk of peritonitis (85,152) and PD cessation (81,83,86,138,148,149). Finally, the worldwide reduction in peritonitis rates could be attributed to international changes in medical practices; notably the use of twin bag disconnection systems, topical exit-site antibiotics and systemic antibiotic prior to catheter insertion (136,139,153,154); which now appear to translate into fewer peritonitis-related transfer to HD.

The lack of improvement in rates of transfer to HD due to catheter issues over time, which remains a leading cause of early PD cessation (81,132,150) has been acknowledged as an important consideration by patients and healthcare professionals (152). Efforts should be made to improve this issue. PD centres should have a multidisciplinary PD access team to reduce primary PD catheter failure and rescue non-functioning catheters (155).

Finally, no change in the rates of transfers to HD due to inadequate dialysis was observed. There is evidence that icodextrin and (in fast peritoneal solute transport rate) APD use can improve peritoneal ultrafiltration and volume control (156–158). We believe that a wider usage of icodextrin, an optimized prescription of APD for fast peritoneal solute transport

rate patients and moving beyond the Kt/V_{urea} dogma (159,160) will avoid inadequacy-related transfers to HD in the absence of uremic symptoms.

We have shown that in France, rates of PD cessation due to either death or transfer to HD, death, and transfer to HD have decreased in recent decades. The decline in transfer to HD rates is mainly due to a significant decline in infection-related transfers, and particularly in self-PD patients.

5. Article

Trends in Peritoneal Dialysis Technique Survival, Death, and Transfer to Hemodialysis: A Decade of Data from the RDPLF

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Keywords

Chronic kidney disease · Peritoneal dialysis · Techniquesurvival · Assistance · Longitudinal trends

Abstract

Introduction: There is limited information on the trends of peritoneal dialysis (PD) technique survival over time. This study aimed to estimate the effect of calendar time on technique survival, transfer to hemodialysis (HD) (and the individual causes of transfer), and patient survival. **Methods:** This retrospective, multicenter study, based on data from the French Language Peritoneal Dialysis Registry, analyzed 14,673 patients who initiated PD in France between January 1, 2005, and December 31, 2016. Adjusted Cox regressions with robust variance were used to examine the probability of a composite end point of either death or transfer to HD, death, and transfer to HD, accounting for the nonlinear impact of PD start time. **Results:** There were 10,201 (69.5%) cases of PD cessation over the study period: 5,495 (37.4%) deaths and 4,706 (32.1%) transfers to HD. The rate of PD ces-

sation due to death or transfer to HD decreased over time (PR 0.96, 95% CI: 0.95–0.97). Compared to 2009–2010, starting PD between 2005 and 2008 or 2011 and 2016 was strongly associated with a lower rate of transfer to HD (PR 0.88, 95% CI: 0.81–0.96, and PR 0.91, 95% CI: 0.84–0.99, respectively), mostly due to a decline in the rate of infection-related transfers to HD (PR 0.96, 95% CI: 0.94–0.98). **Conclusions:** Rates of the composite end point of either death or transfer to HD, death, and transfer to HD have decreased in recent decades. The decline in transfers to HD rates, observed since 2011, is mainly the result of a significant decline in infection-related transfers.

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Introduction

Peritoneal dialysis (PD) is an efficient, cost-effective dialysis modality that enables patients to preserve a high degree of autonomy [1, 2]. However, the main limitation of PD relates to technique survival, which remains a ma-

major concern for ESRD patients and their nephrologists [3, 4]. It has been proposed to define technique survival by the composite end point of death or transfer to hemodialysis (HD) over 2 months [3]. To maximize the amount of information, transfer to HD (death-censored technique survival) and patient survival (transfer to HD censored) should be reported separately. Further, providing information regarding the cause of transfer to HD is critical if one wants to increase PD duration. The causes of transfer to HD could be classified as follows: infection, mechanical causes (catheter dysfunction), inadequate dialysis, social reasons, encapsulating peritoneal sclerosis, and other reasons [3, 5].

Transfer to HD is a barrier toward PD use and could partially explain the low PD prevalence [4]. It has been demonstrated that death is the primary cause of PD cessation [5, 6] and that transfer to HD is mainly due to infection, inadequate dialysis, and catheter dysfunction [3, 6–11].

There are both patient- and center-level characteristics associated with transfer to HD [12–14]. Patient age and comorbidity are associated with death and transfer to HD [12, 15, 16], whereas PD experience (estimated by center size and/or the proportion of dialysis patients treated with PD) has been associated with a lower risk of transfer to HD [12, 14, 17–20]. Other modifiable center characteristics such as icodextrin use [20] and assisted PD programs [21, 22] have been associated with a lower risk of transfer to HD.

The International Society for PD (ISPD) guidelines aim to improve PD usage and technique survival [23, 24]. Significant improvements have been observed in rates of peritonitis cure and relapse since 2010, which led to enhanced technique survival and a decreased occurrence of transfer to HD over this period [12, 20, 25]. Indeed, since 2010, PD cessation due to infections and death declined, whereas PD cessation due to social reasons increased [20]. To our knowledge, only few studies in the literature describe longitudinal trends in PD technique survival [20, 25–27].

This study aimed to estimate the effect of calendar time on technique survival (death or transfer to HD), transfer to HD (death censored), and patient survival (transfer to HD censored). This study was also carried out to evaluate the association between calendar time and the individual causes of transfer to HD over the past decade in France. The secondary objective was to determine whether the calendar time effect on the events of interest was influenced by the assistance status (self-care PD, nurse-assisted PD, and family-assisted PD).

Materials and Methods

Study Population

This was a retrospective study using data from the French Language Peritoneal Dialysis Registry (RDPLF) [28, 29]. Patients older than 18 years starting PD in France between January 1, 2005, and December 31, 2016, were included. The end of the study period was June 20, 2019. No patient was lost to follow-up.

Gender, age at PD start, underlying nephropathy, diabetes mellitus, modified Charlson comorbidity index (CCI) (subtracting the age subscore from the CCI), previous therapy before PD initiation (HD or renal transplantation), and center category (academic, community, nonprofit, and private) were extracted from the registry. The characteristics of the treatment, including suboptimal starters (defined as a period of <30 days on HD before PD initiation) [30], PD modality (continuous ambulatory peritoneal dialysis or automated peritoneal dialysis [APD]), and the use of assistance (through a nurse or family-assisted PD), were obtained from the database. For center size estimation, we calculated the number of incident PD patients per center per year of participation during the study period, as previously reported [31]. Time on PD was calculated in months between the date of PD start and the date of PD cessation (in case of transfer to HD, death, or transplantation) or the end of follow-up (June 20, 2019) if none of these events had occurred.

The complete cohort and a subset of the patients transferred to HD were used for the analysis. In addition, the analyses were performed in the self-care PD, nurse-assisted PD, and family-assisted PD groups.

Events of Interest

PD cessation was the outcome of interest, studied by the occurrence of events of death on PD or transfer to HD for >2 months (composite end point), death on PD (transfer to HD censored), and transfer to HD (death censored) for >2 months. Among the patients transferred to HD, the event of interest was the cause of transfer, studied one at a time. Cause of transfer to HD is a declarative variable collected in the registry. The causes of transfer to HD were classified into the 7 categories adapted from Lan et al. [3]: infection, inadequate dialysis (inadequate ultrafiltration associated with volume overload, inadequate solute clearance associated with uremic syndrome, or poor nutrition), PD catheter issues, social issues (loss of assistance, isolation, and patient preference), encapsulating peritoneal sclerosis, other causes linked with PD, and other causes not linked with PD. Because of the scarcity of encapsulating peritoneal sclerosis, this event was considered a failure due to another cause tied to PD. Of note, time to first event on PD (death or transfer to HD) was modeled. Death occurring on HD shortly after a transfer from PD was not analyzed.

Explanatory Variable

The main explanatory variable was calendar time, or the PD start year, between January 1, 2005, and December 31, 2016.

Statistical Analysis

Categorical variables were described by frequencies and percentages, while continuous variables were described by the median (first and third quartiles). Regression splines were used to explore the functional form of the length of time from the inclusion date until the end of the inclusion period. Transformation of the continuous time variable to a linear or categorical variable was per-

Table 1. Patient characteristics according to the events of interest (*N* = 14,673)

Variables	All patients (<i>n</i> = 14,673)	PD start year 2005–2008	PD start year 2009–2012	PD start year 2013–2016
Age at PD initiation, median (IQR), years	69.6 (55 – 80.2)	70.8 (54.9 – 79.9)	69.4 (54.3 – 80.2)	68.8 (55.6 – 80.3)
Gender (male), <i>n</i> (%)	8,695 (59.3)	2,655 (57.5)	2,706 (58.5)	3,334 (61.4)
Diabetes, <i>n</i> (%)	4,948 (33.7)	1,525 (33)	1,515 (32.8)	1,908 (35.1)
Modified CCI, <i>n</i> (%)				
2	4,632 (31.6)	1,390 (30.1)	1,505 (32.5)	1,737 (32)
3	2,682 (18.3)	851 (18.5)	825 (17.8)	1,006 (18.5)
4	2,436 (16.6)	791 (17.1)	780 (16.9)	865 (15.9)
≥5	4,789 (32.6)	1,477 (32)	1,496 (32.4)	1,816 (33.5)
Missing	134 (0.9)	107 (2.3)	20 (0.4)	7 (0.1)
Underlying nephropathy, <i>n</i> (%)				
Diabetic	2,919 (19.9)	950 (20.6)	895 (19.3)	1,074 (19.8)
Interstitial nephritis	783 (5.3)	242 (5.2)	245 (5.3)	296 (5.4)
Glomerulonephritis	2,109 (14.4)	680 (14.7)	696 (15)	733 (13.5)
Polycystic kidney disease	929 (6.3)	266 (5.8)	323 (7)	340 (6.3)
Unknown	1,659 (11.3)	560 (12.1)	470 (10.2)	629 (11.6)
Uropathy	398 (2.7)	133 (2.9)	128 (2.8)	137 (2.5)
Vascular	4,201 (28.6)	1,339 (29)	1,395 (30.2)	1,467 (27)
Systemic disease	376 (2.7)	134 (2.9)	125 (2.7)	117 (2.2)
Others	1,236 (8.4)	257 (5.6)	342 (7.4)	637 (11.7)
Missing	63 (0.4)	55 (1.2)	7 (0.1)	1
Suboptimal starters, <i>n</i> (%)	1,369 (9.4)	497 (10.8)	434 (9.4)	438 (8.1)
Treatment before PD, <i>n</i> (%)				
No therapy	11,607 (79.1)	3,677 (79.7)	3,671 (79.4)	4,259 (78.4)
HD	2,558 (17.4)	818 (17.7)	783 (16.9)	957 (17.6)
Renal transplantation	482 (3.3)	104 (2.3)	169 (3.7)	209 (3.9)
Missing	26 (0.2)	17 (0.3)	3	6 (0.1)
First PD modality (CAPD), <i>n</i> (%)	11,042 (75.3)	3,408 (73.8)	3,439 (74.3)	4,195 (77.2)
Assistance status, <i>n</i> (%)				
Self-care PD	7,070 (48.2)	2,110 (45.7)	2,236 (48.3)	2,724 (50.2)
Nurse-assisted PD	6,299 (42.9)	1,990 (43.1)	1,974 (42.7)	2,335 (43)
Family-assisted PD	1,304 (8.9)	516 (11.2)	416 (9)	372 (6.8)
Type of center, <i>n</i> (%)				
Community hospital	7,095 (48.4)	2,360 (51.1)	2,220 (48)	2,515 (46.3)
Academic hospital	2,860 (19.5)	898 (19.4)	898 (19.4)	1,064 (19.6)
Nonprofit	3,467 (23.6)	1,097 (23.8)	1,128 (24.4)	1,242 (22.9)
Private hospital	1,251 (8.5)	261 (5.7)	380 (8.2)	610 (11.2)
Center experience, <i>n</i> (%) (new patients per year)				
≤10	8,305 (56.6)	2,578 (55.8)	2,549 (55.1)	3,178 (58.5)
>10	6,368 (43.4)	2,038 (44.2)	2,077 (44.9)	2,253 (41.5)

PD, peritoneal dialysis; IQR, interquartile range; CCI, Charlson comorbidity index; HD, hemodialysis; CAPD, continuous ambulatory peritoneal dialysis.

formed based on the aspect of the graph of the functional form of the predictor.

The odds ratio (OR) can overestimate the prevalence ratio (PR) when the proportion of the event of interest is >10%. The use of PR, estimated with a robust variance's Cox model (instead of OR), has been described as an alternative for the analysis of binary outcomes in longitudinal studies [32].

To explore the association between the time variable and the events of interest, PRs and 95% confidence intervals (CIs) were

calculated using a Cox regression model with robust variance. As recommended, in the Cox model, a constant risk period equal to 1 was assigned to every patient in the cohort [32].

In the complete cohort, the composite end point of death on PD or transfer to HD, death on PD (transfer to HD censored), and transfer to HD (death censored) were the events of interest. The analyses were performed in the self-care PD, nurse-assisted PD, and family-assisted PD subgroups separately.

In the subset of patients transferred to HD, each cause of PD failure was an event of interest (one at a time). The analyses were also carried out in the self-PD, nurse-assisted PD, and family-assisted PD groups separately.

A bivariate analysis was performed to estimate the association between each variable and the events of interest. All variables, including the time variable, were included a priori in the multivariate analysis. Interactions between time and the other covariates were tested in the multivariate models.

Less than 5% of the data on all variables were missing; we assumed the data to be missing at random, enabling us to use a complete case analysis. Analyses were performed with R 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria, including the survival package).

Results

Patient Characteristics

Of the 14,673 incident patients on PD included in the study, 10,201 (69.5%) experienced PD cessation: 5,495 (37.4%) died and 4,706 (32.1%) were transferred to HD over the study period. Causes of transfer to HD were inadequate dialysis (1,853 events, 39%), infection (751, 16%), catheter issues (452, 10%), social issues (366, 8%), other causes linked to PD (579, 12%), and other causes not linked to PD (705, 15%).

The number of patients starting PD per year is displayed in online suppl. Figure 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000515472). The median time on PD was 19 months (interquartile range, 8–35 months). There were 7,070 (48.2%) patients on self-PD, 6,299 (42.9%) patients on nurse-assisted PD, and 1,304 (8.9%) on family-assisted PD. Patients experiencing PD cessation were older, more frequently nurse assisted, and had more comorbidities than the rest of the population. Patient characteristics by PD start year categories are described in Table 1. Incident patients' age and CCI by year of PD start are described in online suppl. Table 1.

Association between Calendar Time and the Proportion of PD Cessation due to Death or Transfer to HD According to the adjusted regression splines, time was linearly associated with the composite end point of death or transfer to HD. Thus, the PD start year was defined as a linear variable in this model. The rate of PD cessation due to death or transfer to HD significantly decreased over time (PR 0.96, 95% CI: 0.95–0.97), regardless of the assistance status (Table 2). Age, gender, diabetes, modified CCI, underlying nephropathy, renal replacement therapy before PD initiation, assistance status, type of center, and center experience were associated with PD

cessation (Table 2). There were no significant interactions between PD start year and the other covariates.

Association between Calendar Time and the Proportion of Death

In the multivariable analyses, time was linearly associated with the rate of death according to the regression splines. Thus, the PD start year was defined as a linear variable in this model. A decline in the death rate was observed over time (PR 0.95, 95% CI: 0.94–0.96), irrespective of assistance status (online suppl. Table 2). Age, gender, diabetes, modified CCI, underlying nephropathy, renal replacement therapy before PD initiation, assistance status, type of center, and center experience were associated with death (online suppl. Table 2). There were no significant interactions between PD start year and the other covariates.

Association between Calendar Time and the Proportion of Transfer to HD

Based on the shape of the regression spline, the PD start year for this part of the analysis was transformed into a categorical variable composed of 3 classes: 2005–2008, 2009–2010 (reference class), and 2011–2016 (online suppl. Fig. 2). In the adjusted analyses, starting PD in 2005–2008 or 2011–2016 was strongly associated with a decreased rate of transfer to HD (PR 0.88, 95% CI: 0.81–0.96, and PR 0.91, 95% CI: 0.84–0.99, respectively) (Table 3). The PR change over time followed a similar pattern in nurse-assisted PD patients and self-care PD patients (online suppl. Fig 2).

Age, gender, diabetes, modified CCI, a suboptimal start, therapy before PD initiation, and assistance status were associated with transfer to HD (Table 3). There were no significant interactions between PD start year and the other covariates.

Association between Calendar Time and the Different Causes of Transfer to HD

In the multivariate analyses, time was linearly associated with a transfer to HD for infection and for other causes not linked to PD (online suppl. Fig. 3; Table 4). The proportion of transfer to HD for infections decreased over time (PR 0.96, 95% CI: 0.94–0.98), whereas it increased for other causes not linked to PD (PR 1.05, 95% CI: 1.03–1.08). The PR change over time followed a similar pattern in self-care PD patients, but not in nurse nor family-assisted PD patients. Transfer to HD for catheter issues increased over time for patients on family-assisted PD (PR 1.16, 95% CI: 1.04–1.29) (Table 4). There was no association between PD start year and the other causes of transfer to HD.

Table 2. Association between PD start year and the prevalence ratio of the composite end point (death or transfer to HD), adjusting for patient characteristics, for each type of assistance and self-care PD

Explanatory variable	All patients (n = 14,673) PR (95% CI)	Nurse-assisted (n = 6,299) PR (95% CI)	Family-assisted (n = 1304) PR (95% CI)	Self-care (n = 7,070) PR (95% CI)
PD start year (2005–2016), for a year increase	0.96 (0.95–0.97)	0.95 (0.94–0.96)	0.96 (0.95–0.98)	0.97 (0.96–0.98)
Age, for a 10-year increase	1.18 (1.16–1.20)	1.10 (1.08–1.13)	1.17 (1.11–1.22)	1.20 (1.17–1.23)
Gender, female	0.92 (0.89–0.95)	0.90 (0.86–0.94)	0.96 (0.87–1.06)	0.94 (0.88–1.01)
Diabetes	1.09 (1.04–1.14)	1.05 (0.99–1.12)	1.08 (0.95–1.23)	1.17 (1.07–1.29)
Modified CCI				
2	Reference	Reference	Reference	Reference
3	1.24 (1.17–1.31)	1.03 (0.96–1.12)	1.21 (0.98–1.48)	1.31 (1.19–1.43)
4	1.32 (1.24–1.40)	1.05 (0.97–1.14)	1.32 (1.09–1.61)	1.47 (1.33–1.63)
≥5	1.43 (1.35–1.51)	1.11 (1.03–1.19)	1.37 (1.14–1.65)	1.77 (1.61–1.95)
Suboptimal starters	0.98 (0.93–1.04)	1.02 (0.95–1.10)	0.90 (0.75–1.07)	0.98 (0.87–1.10)
Underlying nephropathy				
Polycystic kidney disease	Reference	Reference	Reference	Reference
Diabetes	1.46 (1.29–1.62)	1.15 (0.95–1.40)	1.60 (0.99–2.55)	1.37 (1.17–1.61)
Interstitial nephritis	1.22 (1.07–1.39)	0.94 (0.75–1.17)	1.48 (0.88–2.49)	1.24 (1.03–1.48)
Glomerulonephritis	1.26 (1.13–1.41)	1.16 (0.95–1.42)	1.30 (0.80–2.12)	1.26 (1.10–1.44)
Unknown	1.44 (1.29–1.61)	1.15 (0.95–1.39)	1.41 (0.87–2.27)	1.48 (1.29–1.72)
Uropathy	1.33 (1.13–1.56)	1.03 (0.78–1.35)	1.91 (1.08–3.38)	1.35 (1.08–1.67)
Vascular	1.47 (1.32–1.63)	1.18 (0.98–1.42)	1.50 (0.94–2.37)	1.48 (1.29–1.70)
Systemic disease	1.35 (1.15–1.58)	1.12 (0.86–1.47)	1.24 (0.66–2.34)	1.35 (1.09–1.67)
Others	1.45 (1.29–1.63)	1.15 (0.94–1.40)	1.85 (1.15–2.98)	1.43 (1.21–1.68)
Therapy before PD initiation				
No therapy	Reference	Reference	Reference	Reference
HD	1.17 (1.12–1.23)	1.12 (1.06–1.19)	1.05 (0.92–1.19)	1.28 (1.18–1.39)
Transplantation	1.33 (1.18–1.51)	0.83 (0.59–1.18)	1.48 (1.01–2.18)	1.47 (1.29–1.68)
Assistance status				
Self-care	Reference			
PD	1.35 (1.29–1.42)	na	na	na
Nurse-assisted PD				
Family-assisted PD	1.37 (1.29–1.46)	na	na	na
Type of center				
Academic hospital	Reference	Reference	Reference	Reference
Community hospital	1 (0.95–1.05)	0.98 (0.92–1.04)	1.02 (0.89–1.17)	1.02 (0.94–1.11)
Nonprofit	0.94 (0.90–0.99)	0.97 (0.90–1.04)	0.99 (0.85–1.15)	0.89 (0.81–0.98)
Private hospital	1.08 (1.01–1.16)	1.12 (1.02–1.22)	1.06 (0.87–1.31)	1.05 (0.93–1.20)
Center experience (new patients per year)				
≤10	Reference	Reference	Reference	Reference
>10	1.07 (1.03–1.11)	1.02 (0.97–1.07)	1.15 (1.04–1.28)	1.11 (1.04–1.19)

PR, prevalence ratio; PD, peritoneal dialysis; CCI, Charlson comorbidity index; HD, hemodialysis; na, nonapplicable.

Association between Calendar Time and the Proportion of Transplantation

Transplantation rates remained stable over the study period. In the multivariate analysis, no association between calendar time and the proportion of transplantation was observed (PR 0.99, 95% CI: 0.98–1.02), irrespective of assistance status. Age, diabetes, modified CCI, underlying nephropathy, therapy before PD initiation, and assistance status were associated with transplantation

(data not shown). There was no association between PD start year and the other covariates.

Discussion

Technique survival remains a major concern for individuals with ESRD, dialysis patients, and their nephrologists [3, 4, 33]. We describe the trends of PD cessation due

Table 3. Association between PD start year and the prevalence ratio of transfer to HD, adjusting for patient characteristics, for each type of assistance and self-care PD

Explanatory variable	All patients (n = 14,673)	Nurse- assisted(n = 6,299)	Family-assisted (n = 1,304)	Self-care (n = 7,070)
PD start year (category)				
2009–2010	Reference	Reference	Reference	Reference
2005–2008	0.88 (0.81–0.96)	0.84 (0.72–0.97)	0.99 (0.74–1.34)	0.89 (0.79–0.99)
2011–2016	0.91 (0.84–0.99)	0.87 (0.75–0.99)	0.99 (0.75–1.32)	0.91 (0.82–1.01)
Age, for a 10-year increase	0.93 (0.91–0.95)	0.78 (0.75–0.81)	0.82 (0.77–0.88)	1.01 (0.97–1.03)
Gender, female	0.92 (0.86–0.97)	0.96 (0.87–1.06)	0.81 (0.66–0.99)	0.93 (0.86–1.01)
Diabetes	1.18 (1.08–1.30)	1.26 (1.09–1.47)	0.93 (0.69–1.27)	1.15 (1.01–1.32)
Modified CCI				
2	Reference	Reference	Reference	Reference
3	1.15 (1.06–1.26)	0.86 (0.72–1.07)	1.11 (0.78–1.58)	1.19 (1.07–1.33)
4	1.17 (1.06–1.26)	0.92 (0.78–1.09)	0.71 (0.48–1.04)	1.22 (1.08–1.39)
≥5	1.03 (0.94–1.14)	0.67 (0.57–0.80)	0.92 (0.66–1.29)	1.21 (1.06–1.37)
Suboptimal starters	0.87 (0.78–0.96)	0.90 (0.76–1.07)	0.83 (0.58–1.19)	0.89 (0.78–1.03)
Underlying nephropathy				
Polycystic kidney disease	Reference	Reference	Reference	Reference
Diabetes	1.27 (1.08–1.48)	0.90 (0.64–1.26)	1.22 (0.64–2.33)	1.28 (1.05–1.55)
Interstitial nephritis	1.11 (0.94–1.31)	0.77 (0.52–1.14)	0.78 (0.38–1.62)	1.18 (0.97–1.43)
Glomerulonephritis	1.09 (0.95–1.25)	1.09 (0.77–1.56)	0.69 (0.36–1.34)	1.14 (0.98–1.33)
Unknown	1.17 (1.01–1.35)	0.89 (0.64–1.25)	0.82 (0.43–1.54)	1.22 (1.03–1.45)
Uropathy	1.02 (0.83–1.26)	0.84 (0.51–1.37)	0.66 (0.28–1.56)	1.07 (0.85–1.36)
Vascular	1.10 (0.96–1.26)	0.83 (0.60–1.14)	0.75 (0.41–1.37)	1.19 (1.02–1.39)
Systemic disease	1.10 (0.90–1.35)	1.02 (0.64–1.64)	0.44 (0.14–1.32)	1.15 (0.91–1.45)
Others	0.83 (0.71–0.98)	0.56 (0.39–0.81)	0.51 (0.26–1.02)	0.96 (0.79–1.16)
Therapy before PD initiation				
No therapy	Reference	Reference	Reference	Reference
HD	1.24 (1.16–1.34)	1.12 (0.99–1.28)	0.98 (0.76–1.25)	1.33 (1.21–1.46)
Transplantation	1.53 (1.34–1.76)	1.12 (0.71–1.79)	1.34 (0.62–2.89)	1.61 (1.40–1.87)
Assistance status				
Self-care	Reference	na	na	na
PD	0.63 (0.58–0.68)	na	na	na
Nurse-assisted PD		na	na	na
Family-assisted PD	0.79 (0.70–0.88)	na	na	na
Type of center				
Academic hospital	Reference	Reference	Reference	Reference
Community hospital	1.02 (0.94–1.10)	1.01 (0.87–1.17)	0.96 (0.71–1.29)	1.02 (0.92–1.13)
Nonprofit	1 (0.92–1.09)	1.01 (0.86–1.19)	1.26 (0.93–1.71)	0.95 (0.85–1.06)
Private hospital	1.11 (0.99–1.25)	1.07 (0.86–1.33)	1.19 (0.77–1.85)	1.15 (0.98–1.34)
Center experience (new patients per year)				
≤10	Reference	Reference	Reference	Reference
>10	0.95 (0.89–1.01)	0.83 (0.75–0.93)	0.96 (0.77–1.20)	1.02 (0.94–1.10)

PR, prevalence ratio; PD, peritoneal dialysis; CCI, Charlson comorbidity index; HD, hemodialysis; na, nonapplicable.

to the 3 most major outcomes – death or transfer to HD, death (transfer to HD censored), and transfer to HD (death censored) – and the cause of transfer to HD over a decade in a country where PD has been available for >30 years and where assisted PD is fully covered by health insurance. Our study shows that PD cessation (due to either death or transfer to HD) and death (transfer to HD censored)

followed a similar pattern. Both declined linearly over time, without any differences in whether patients were autonomous or assisted (Table 2; online suppl. Table 2). Death-censored transfer to HD peaked starting in 2009 and lasted through 2010 before declining over the period from 2011 to 2016. This declining rate of transfer to HD starting in 2011 was not observed in family-assisted PD

Table 4. Association between PD start year (between 2005 and 2016) and the prevalence ratio of each cause of transfer to HD, for each type of assistance and self-care PD

Causes of transfer to HD	All patients(<i>n</i> = 4,706) PR (95% CI)	Nurse-assisted(<i>n</i> = 1,530) PR (95% CI)	Family-assisted (<i>n</i> = 404) PR (95% CI)	Self-care (<i>n</i> = 2,772) PR (95% CI)
Adequacy	1 (0.99–1.01)	0.98 (0.96–1.01)	0.99 (0.95–1.04)	1.01 (0.99–1.03)
Infection	0.96 (0.94–0.98)	0.98 (0.94–1.02)	1.03 (0.96–1.10)	0.94 (0.91–0.96)
Catheter issues	1.03 (0.99–1.06)	1.04 (0.99–1.09)	1.16 (1.04–1.29)	1 (0.96–1.04)
Other causes linked to PD	0.98 (0.96–1.01)	0.99 (0.95–1.03)	0.93 (0.85–1.02)	0.97 (0.94–1.01)
Other causes not linked to PD	1.05 (1.03–1.08)	1.04 (0.99–1.07)	1.03 (0.94–1.12)	1.07 (1.03–1.10)
Social	0.98 (0.95–1.02)	0.97 (0.92–1.01)	0.94 (0.84–1.05)	1.01 (0.97–1.06)

Multivariate Cox regression with robust variance modeling PD start year as a linear variable between 2005 and 2016, adjusted for patient characteristics. PR, prevalence ratio; PD, peritoneal dialysis; HD, hemodialysis.

patients (online suppl. Fig. 1). Transplantation rates remained stable over the study period.

Our findings are in line with previous research. Schaubel et al. [34] described a reduced rate of transfer to HD for the 1990–93, 1994–95, and 1996–97 calendar periods compared to 1981–89. Htay et al. [20] observed a significant reduction in the occurrence of the composite end point of death or transfer to HD (hazard ratio [HR] of 0.87, 95% CI: 0.82–0.93) and death-censored transfer to HD (HR 0.93, 95% CI: 0.86–0.99) between the periods 2004–2009 and 2010–2014. Perl et al. [26] observed an improvement in PD patient survival between 1995 and 2009 but only small changes in PD technique survival. More recently, Sukul et al. [25] reported an increase in technique survival between 1996 and 2011, since the rates of death and transition to HD declined over this time period.

In our study, the decline in the proportion of transfers to HD observed since 2011 was mainly due to a significant decline in transfers resulting from infections, particularly in self-PD patients (online suppl. Fig. 3; Table 4). Similar findings have been described [8, 20, 34]. In a study by Htay et al. [20], the hazards of transfers to HD due to infections decreased annually since 2010 (HR 0.64, 95% CI: 0.57–0.72). There is abundant evidence that peritonitis risk has decreased over time [8, 35, 36]; when parallel, the rates of peritonitis cure improved [12].

The enhancement of trainings and educational programs over the past decade may partly explain this finding. In support of that, the declining rate over time of infection-related transfers to HD has primarily been observed in self-PD patients. Multidisciplinary educational programs, including training to perform good hand hygiene while carrying out PD exchanges, are associated with a lower peritonitis rate [37, 38] and are now largely recommended

[23, 39]. The risk of peritonitis could also be reduced with a home visit before PD initiation, as it may be useful for detecting problems [40, 41], and routine evaluations of patient retraining needs [42]. The systematic usage of hydroalcoholic solutions for hand hygiene in dialysis centers in France was introduced between 2010 and 2011. This measure may have impacted the peritonitis rate [43].

Center-level characteristics contribute substantially to the marked variation in peritonitis rates and outcomes that exist across PD centers. Previous studies have demonstrated variation in peritonitis rates across PD centers [9, 10]. Both center size [18, 19, 21, 25, 44, 45] and experience [14, 46] impact PD outcomes. Patients initiating PD in higher volume centers have a lower risk of peritonitis [20, 33] and PD cessation [4, 14, 18, 19, 25, 46]. As peritonitis is one of the leading causes of transfer to HD, a center's experience and practices could directly affect technique survival. This was shown in a recent study by Htay et al. [20] where centers with higher proportions of patients receiving PD (>29% patients receiving PD) had a significantly and independently lower risk of peritonitis-related transfers to HD (OR 0.78; 95% CI: 0.62–0.97). Nevertheless, even though peritonitis rates declined in the period of 2010 through 2014 compared to 2004 through 2009, no differences in the odds of transfers to HD were observed over time. Variation in peritonitis cure by antibiotics across centers was reduced by 66% after adjusting for center-level characteristics, suggesting that centers' practices account for divergences in peritonitis outcomes [33]. Indeed, in another study by the same team, centers' practices such as poorer center achievement of target phosphate, lower center APD exposure, and antifungal use (higher or lower use compared to average use) have been associated with higher hazards of

infection-related transfers to HD [20]. Finally, the number of patients on PD slightly increased over the study period (online suppl. Fig. 1), which could have enabled a growing experience of PD in some centers.

Finally, improvements in PD utilization have been witnessed in the past decade. The use of twin bag disconnection systems, systemic antibiotic administration prior to catheter insertion, topical exit-site or nasal antibiotics, and antifungal prophylaxis have proved useful in reducing peritonitis risk [13, 23, 35, 47]. The worldwide reduction in peritonitis rates has been attributed to these inter-national changes in medical practices, which now appear to translate into fewer peritonitis-related transfers to HD. We found no improvement in rates of transfer to HD due to catheter issues over time; exacerbation was even noted in family-assisted patients. This finding is consistent with previous research [8, 20]. In the study by Htay et al. [20], the risk of mechanical-related transfers to HD did not differ in the time period 2010–2014 compared to 2004–2009 (HR 0.93, 95% CI: 0.80–1.09) [20]. The worsening over time of transfers to HD due to catheter issues in family-assisted PD patients could reflect a decrease in caregivers' involvement. A preceding study by our team found a linear decline in family-assisted PD use over time, notably among others, because of a modification in the state of caregivers' health [48]. Catheter complications, a leading cause of early PD cessation [8, 14, 44], have been acknowledged as an important consideration by patients and healthcare professionals [33]. Efforts should be made to improve this issue. Every PD center should have a multidisciplinary PD access team (including surgeons, nurses, and nephrologists) to reduce primary PD catheter failure and to rescue nonfunctioning catheters [49]. Close cooperation between enthusiastic nephrologists and surgeons should be further encouraged.

Inadequate dialysis is defined by either ultrafiltration failure associated with volume overload or inadequate solute clearance associated with uremic syndrome [3]. In our work, no change in the rates of transfers to HD due to inadequate dialysis was observed, which is consistent with previous studies [20]. Of note, icodextrin has been available in France throughout the study period. Rates of continuous ambulatory peritoneal dialysis transfer to HD for inadequate dialysis increased after 1990 according to Schaubel et al. [34]. Center-level characteristics such as center size, icodextrin usage, and APD exposure have been associated with technique survival, but not specifically with inadequate dialysis [20]. There is evidence that icodextrin and (in high transporters) APD use can improve peritoneal ultrafiltration and volume control [50–

52]. We believe that a wider usage of icodextrin and an optimized prescription of APD for high transporter patients could decrease transfers to HD due to ultrafiltration failure and volume overload. Since there is inconclusive evidence that targeting a higher peritoneal Kt/V_{urea} translates into improved PD outcomes, the achievement of a specific clearance target is no longer recommended [53]. It can be hypothesized that moving beyond the Kt/V_{urea} dogma will avoid inadequacy-related transfers to HD in the absence of uremic symptoms in the future.

Transfers to HD due to other reasons not linked to PD increased over time in our study. This temporal trend could be explained by factors that were not examined. For instance, socioeconomic status and disability could influence the risk of transfer to HD but are not captured by the registry. Further studies are needed to investigate this question.

Older age, diabetes, a higher CCI, and underlying nephropathy were associated with an increased probability of death and transfer to HD, likely a reflection of increased comorbidity and frailty. Assisted PD was associated with a higher risk of death and a lower risk of transfer to HD. Similar findings have been described previously [14, 21, 25]. No temporal trends of the impact of assistance on patient and technique survival were observed in our study; this impact remained stable over time. A suboptimal start was associated with a decreased risk of transfer to HD. One explanation could be that suboptimal starters, by definition, start RRT on HD to later transfer to PD once they have received the information on RRT modalities. As these patients have already experimented HD, they might be more reluctant to transfer to HD in case of PD failure or have contraindication to HD (vascular access or hemodynamic complication). However, this result should be interpreted with caution as <10% of the patients were considered as having “suboptimal start.”

Our study has some limitations. The observational design cannot lead to conclusions regarding causality. The retrospective nature of registry is associated with classification bias. As the causes of PD technique failure are declarative in the registry, this could lead to declaration bias. Residual confounders, such as residual kidney function and detailed information of PD prescription and educational programs, are optionally declared in the registry and thus not fully captured, even though these factors are known to impact technique survival.

In conclusion, this study shows that in France, rates of the composite end point of either death or transfer to HD, death, and transfer to HD have decreased in recent decades. The decline in transfer to HD rates observed since

2011 is mainly due to a significant decline in infection-related transfers, particularly in self-PD patients, but which was not observed in assisted PD patients. Since no change in the rates of transfers due to catheter issues and inadequate dialysis was noted, we suggest that efforts should now focus on both of these issues.

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Statement of Ethics

The RDPLF has the approval of the French National Ethics Committee (Commission nationale de l'informatique et des libertés). This study took place within the framework of this authorization.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Annabel Boyer designed the study, interpreted the data, and drafted the manuscript. Antoine Lanot, Mark Lambie, Christian Verger, and Sonia Guillouët revised the manuscript and provided intellectual content of critical importance. Thierry Lobbedez and Clémence Béchade designed the study and analyzed the data.

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VI. Time spent on HD before transitioning to PD impacts PD outcomes

1. Introduction

Even though, as previously demonstrated, transfers from PD to HD tend to decrease over time, transfer to HD remains a major cause of PD cessation. Overall, a significant proportion of patients, which can be as much as one-third, who undergo KRT will transfer from one dialysis modality to another (37). The patients' treatment pathway is now considered as "integrated care" and includes a succession of different dialysis modalities rather than a single one, transition periods being periods at risk for the patient if they are unplanned (37,39,161). The transition from PD to HD is one of the most common transitional periods during patients' pathways and this transition has largely been studied (162).

A much smaller proportion of patients will experience a transfer from HD to PD, because of the patients' preferences or the exhaustion of vascular access or bad tolerance of HD sessions (44,53,163–167). The outcome of patients transferred from HD to PD in comparison with patients starting with PD as first KRT remains controverted (150,157,166–168). One could expect that the time spent on HD before transitioning to PD would impact PD outcomes; however, to our knowledge, this has never been described in the literature.

We conducted a registry-based study aiming to report the effect of transitioning from HD on PD technique survival (death or retransfer to HD), death (retransfer-to-HD censored), and retransfer to HD (death censored), accounting for the effect of time spent on HD before transitioning to PD.

2. Materials and methods

For this final part of the thesis, data from the REIN registry was used. All patients older than 18 years who began HD between 1st January 2008 and 31 December 2016 were extracted

from the database. From those, patients who experienced a transfer from HD to PD during the observation period were included in the study. Of note, patients experiencing renal recovery or renal transplantation between HD and PD were not included in the study.

The main explanatory variable, time spent on HD before transfer to PD, corresponded to the time between HD start and PD start, in months. Patients' comorbidities and characteristics of HD and PD treatment were extracted from the registry.

All patients included in the study were followed until 31 December 2019 or the occurrence of any of the following events: death (including palliative care), retransfer to HD, kidney transplantation, or renal recovery. Events of interest were PD cessation, studied by the occurrence of events of death on PD or retransfer to HD (composite endpoint), death on PD (retransfer-to-HD censored), and retransfer to HD (death censored). Competing events were transplantation and renal function recovery. For each patient, survival time was defined by the length of time between PD initiation and any of the events of interest, competing events, or end of follow-up.

Regression splines were used to explore the possibility that our main explanatory variable, time spent on HD before transfer to PD, did not respect the log linearity assumption. Transformation of this continuous variable to a linear or categorical variable was performed based on the aspect of the graph of the functional form of the predictor (169), and fractional polynomial transformation was explored (92).

To explore the association between the time spent on HD and the events of interest, cs-HRs were estimated using a Cox regression model. For competing events, sd-HRs were obtained by performing a Fine and Gray competing risks regression model. The uncertainty of the results was expressed with 95% CIs (105,107).

Data were missing for several variables, with more than 10% missing values for three variables. A complete case analysis would have excluded 836 patients (42%) from the dataset. Multiple imputation by chained equation (MICE) was performed, imputing 50 sets of missing values.

3. Results

Of the 77,587 patients who started HD between 2008 and 2016, 1985 (3%) were transferred to PD and thus included in the study. Among these HD to PD transitions, 1344 (68%) occurred within the first 3 months on HD. During the study period, there were 732 (37%) deaths, 732 (37%) retransfers to HD, 313 (16%) transplants, and 62 (3%) renal function recoveries. The median time until death or retransfer to HD was 20 (IQR 18-21) months.

Time spent on HD before transfer to PD (for 1 month increase) was significantly associated with a higher occurrence of death or retransfer to HD (cs-HR 1.01, 95% CI 1.00-1.02) and of death censored on retransfer to HD (cs-HR 1.02, 95%CI 1.01-1.03). It was linearly modelled, without polynomial transformation being required for the variable time spent in HD. However, it was not associated with retransfer to HD censored on death (cs-HR 1.00, 95%CI 0.99-1.01).

When considering competing events, Cox and Fine and Gray regression models provided similar results.

4. Discussion

We have shown that the time spent on HD before transfer to PD is associated with an increased risk of PD cessation due to death or retransfer to HD (composite endpoint) and

death (retransfer-to-HD censored). The effect of the time spent on HD on PD outcomes seemed to increase constantly with increasing time spent on HD.

In the few studies describing this transition, time spent on HD before PD is usually considered as a categorical variable divided into early and late transfers. The threshold used to distinguish them is often 3 months. The motivation for the transfer seems to be drastically different depending on its timing, early transfers being motivated by the patient's choice in a context of unplanned arrivals, whereas late transfers may result from exhaustion of vascular access or bad tolerance of HD sessions (44,53,163–167). In our study, it appears that linear modelling best described the association between the time spent on HD before transfer and PD outcomes. We can thus assume that the effect of the time spent on HD before transfer on the risk of PD cessation appears from the initiation of HD and increases gradually over time. If a transfer to PD is considered for a patient on HD, it should be prepared and performed as soon as possible after HD initiation to limit the time spent on HD.

Another particularity of our study lies in the fact that all patients transferred from HD to PD were included in our study, regardless of the time spent on HD, while the majority of the previous studies excluded patients staying less than 3 months on HD (44,163,165–167). The majority (68%) of our transfers occurred early, within the first 3 months after HD initiation. Excluding early transfers could have led to a significant underestimation of the incidence of HD-to-PD transfer and its underlying effects. In our opinion, future research should include HD-to-PD transfers regardless of the time spent on HD.

Transitions between dialysis modalities is a period at risk (150) and could have a direct impact on patient survival. The fact that time spent on HD before transfer to PD was linearly associated with PD outcomes suggests not only an effect of the transition but also an effect of the time spent on HD. In light of our results, it appears that for each year spent on HD, the

increased risk of mortality is even greater for patients transferring to PD than for patients remaining on HD. Surprisingly, time spent on HD was not associated with retransfer to HD, even though the event of transfer has previously been associated with a higher risk of PD technique failure compared to patients starting KRT with PD (150,168).

In conclusion, this final part of the thesis shows that the transition from HD to PD is a rare event, since only 3% of patients beginning on HD were transferred to PD in our study, which happens early in the course of KRT, mostly within the first 3 months. Time spent on HD before transfer to PD impacts patient survival but does not impact retransfer to HD, and importantly the effect of the time spent on HD on the risk of PD cessation seems to increase gradually over time.

5. Article (submitted)

Time spent on hemodialysis before transitioning to peritoneal dialysis impacts peritoneal dialysis outcomes

Running title: Transition from hemodialysis to peritoneal dialysis

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Abstract

Background and objectives: Transitions between dialysis modalities are frailty periods for patients. Data on transitioning from HD (hemodialysis) to PD (peritoneal dialysis) are controversial. We hypothesized that time spent on HD before transfer to PD has an impact on PD outcomes.

Design, setting, participants, and measurements: This registry-based, nationwide study analyzed patients transferred from HD to PD. Patients who began HD between January 2008 and December 2016 were included. Cox and Fine and Gray regression models were used to explore the relationship between time spent on HD before PD and outcomes in PD: PD cessation for death or retransfer to HD (composite endpoint); for death (censored on retransfer to HD); and for retransfer to HD (censored on death).

Results: Over the study period, 1985 patients started HD and were then transferred to PD. The median time spent on HD before transfer to PD was 1.94 months (interquartile range (IQR) 1.02-4.01). The median survival time on PD after this transition was 20 months (IQR 18-21) when considering composite endpoint death or retransfer to HD. Time spent on HD before PD was associated with increased risk of PD cessation for death or retransfer to HD (cause-specific hazard ratio (cs-HR) 1.01, 95% confidence interval (CI) 1-1.02 for a 1-month increase) and risk of death (cs-HR 1.02, 95%CI 1.01-1.03). It was not associated with retransfer to HD censored on death (cs-HR 1.00, 95%CI 0.99-1.01). The results were similar when considering competing events in a Fine and Gray model. Time spent on HD before PD was modeled as a linear covariate.

Conclusion: Time spent on HD before transfer to PD is associated with patient survival but not with retransfer to HD. The effect of the time spent on HD on PD outcomes seemed to increase constantly with increasing time spent on HD.

Introduction

A significant proportion of patients, which can be as much as one-third, who undergo renal replacement therapy (RRT) will transfer from one dialysis modality to another (1). The patients' treatment pathway is now considered as "integrated care" and includes a succession of different dialysis modalities rather than a single one. According to the Renal Epidemiology Information Network (REIN) registry, 13% of incident patients on peritoneal dialysis (PD) were transferred to hemodialysis (HD) within the first 2 years, and 21% of patients treated by PD 2 years after RRT initiation had previously been treated by HD (1,2).

The transition from PD to HD is one of the most common transitional periods during patients' pathways, and up to 35% of patients on PD will experience a transfer to HD (3). Although much remains unknown, this transition has largely been studied. In addition, transitions from a dialysis modality to another can be periods at risk for the patient if they are unplanned (1,4,5).

A much smaller proportion of patients will experience a transfer from HD to PD. There seem to be two different stages in this type of transition: one within the first two months, reflecting patients' preferences, and a second one later on due to exhaustion of vascular access or bad tolerance of HD sessions (6-12). There is controversy about the outcome of patients transferred from HD to PD in comparison with patients starting with PD as the first RRT (13). Technique failure and mortality rates of patients transferred from HD to PD have been found to be higher than those of patients starting RRT directly on PD (8,11,14,15). However, other studies suggested that the outcomes of these patients did not differ from those of patients starting with PD as the first RRT (7,9,10,12). Notably, in most of these studies, patients transferred from HD to PD were defined as those who had been treated with HD for at least 3 months before switching to PD, without considering a shorter period of

HD treatment before PD start. Only two of these studies were based on data from registries (8,14), while others reported monocentric experiences.

One could expect that the time spent on HD before transitioning to PD would impact PD outcomes; however, to our knowledge, this has never been described in the literature. Interestingly, when studying PD technique survival, the definition of the outcome of interest can change across the studies. Lan et al. proposed a standardized definition, using a composite endpoint of death or transfer to HD. To maximize the amount of information, death (transfer-to-HD censored) and transfer to HD (death censored) should be separately reported (16).

This registry-based study aimed to report the effect of transitioning from HD on PD technique survival (death or retransfer to HD), death (retransfer-to-HD censored), and retransfer to HD (death censored), accounting for the effect of time spent on HD before transitioning to PD.

Materials and methods

Study population

This was a retrospective study using data from the REIN registry. All patients older than 18 years who began HD between 1st January 2008 and 31 December 2016 were extracted from the database. From those, patients who experienced a transfer from HD to PD during the observation period were included in the study. Of note, patients experiencing renal recovery or renal transplantation between HD and PD were not included in the study. The end of the study period was 31 December 2019.

Definition of variables

The main explanatory variable, time spent on HD before transfer to PD, corresponded to the time between HD start and PD start, in months.

Sex, age at HD start, body mass index (BMI), underlying nephropathy, diabetes mellitus, cardiovascular disease (defined as the following conditions: stroke or transient ischemic attack, dysrhythmia, peripheral vascular disease, coronary heart disease), congestive heart failure, chronic respiratory disease, cirrhosis, and active cancer were extracted from the database. Characteristics of HD treatment, including emergency start, start on catheter, and erythropoiesis-stimulating agent (ESA) use at HD initiation, were also extracted. Concerning PD treatment, PD modality (continuous ambulatory PD [CAPD] or automated PD [APD]) and the use of assistance were obtained from the database. Underlying nephropathy is composed of the following classes: autosomal dominant polycystic kidney disease (APKD), diabetes, glomerulonephritis, vascular renal disease, unknown, and others.

Events of interest

All patients included in the study were followed until 31 December 2019 or the occurrence of any of the following events: death (including palliative care), retransfer to HD, kidney transplantation, or renal recovery.

Events of interest were PD cessation, studied by the occurrence of events of death on PD or retransfer to HD (composite endpoint), death on PD (retransfer-to-HD censored), and retransfer to HD (death censored). Competing events were transplantation and renal function recovery. For each patient, survival time was defined by the length of time between PD initiation and any of the events of interest, competing events, or end of follow-up.

Patients lost to follow-up were censored at the latest available date.

Statistical analysis

Continuous variables were described by medians (first and third quartiles), while categorical variables were described by frequencies and percentages. Based on spline visualization from Cox model regression, age did not meet the assumption of log linearity and was divided into classes of clinical importance: 18-40 years old; 40-60 years old; 60-80 years old; and > 80 years old.

Time spent on HD before transfer to PD was our main explanatory variable of interest. Regression splines were used to explore the possibility that it did not respect the log linearity assumption. Transformation of this continuous variable to a linear or categorical variable was performed based on the aspect of the graph of the functional form of the predictor (17), and fractional polynomial transformation was explored (18).

To explore the association between the time spent on HD and the events of interest, cause-specific hazard ratios (cs-HRs) were estimated using a Cox regression model. For competing events, subdistribution hazard ratios (sd-HRs) were obtained by performing a Fine and Gray competing risks regression model. The uncertainty of the results was expressed with 95% confidence intervals (CIs). For the cs-HR, the risk set decreases at each time point at which there is a PD cessation for a cause other than death or retransfer to HD (events that are not the events of interest are censored), measuring the specific association between the variable and the event of interest. For the sd-HR, patients experiencing PD cessation for an event other than the one under consideration remain in the risk set, assessing the net association between the variable and all possible events (19,20). All variables considered relevant were included *a priori* in the multivariate analyses. Interactions between age-sex, time in HD-age, and time in HD-cardiovascular disease were tested in the multivariate models.

Data were missing for several variables, with more than 10% missing values for three variables (BMI, ESA use at HD start, and nurse assistance). A complete case analysis would

have excluded 836 patients (42%) from the dataset. Multiple imputation by chained equation (MICE) was performed, imputing 50 sets of missing values (21). A Cox model regression analysis on complete cases and then a pooling analysis of the estimate effect was conducted on the 50 imputed datasets. Complete case analysis was used for the Fine and Gray regression models. BMI, with 20% missing values, was excluded from this part of the analysis so that complete case analyses excluded 632 patients (32%).

Analyses were performed with R software, version 3.6.3 (R Foundation for Statistical Computing, Vienna Austria, including the survival and cmrpsk packages).

Results

Patient characteristics

Of the 77,587 patients who started HD between 2008 and 2016, 1985 (3%) were transferred to PD. We excluded 469 patients under 18 years of age.

Patient characteristics at baseline are presented in Table 1. HD to PD patients, compared to patients who remained on HD, seemed to be younger (median age 67.67 vs 71.2, respectively) and less comorbid. They also started HD in emergency situations (51% vs 31%) and on catheters (85% vs 52%) more frequently and had less ESA at HD initiation (34% vs 40%). Other characteristics were comparable, including the frequency of cardiovascular disease.

The 75,133 patients not experiencing transfer to PD were removed for the subsequent analysis (Supplemental Figure 1). For the 1985 patients included in our study, the median time spent on HD before transfer to PD was 1.94 months (IQR 1.02-4.01). CAPD was the modality used by 1374 (69%) patients, and 989 (50%) were nurse-assisted. Among these HD

to PD transitions, 1344 (68%) occurred within the first 3 months on HD. The distribution of time spent on HD is shown in Figure 1.

Causes of PD cessation

During the study period, there were 732 (37%) deaths, 732 (37%) retransfers to HD, 313 (16%) transplants, and 62 (3%) renal function recoveries. At the end of the observation period, 140 (7%) patients were still on PD. Only 6 patients were lost to follow-up. The cumulative incidental functions of these events are presented in Figure 2.

PD cessation for death or retransfer to HD (composite endpoint)

The median time until death or retransfer to HD was 20 (IQR 18-21) months (Supplemental Figure 2).

In the multivariable analysis (Figure 3A), time spent on HD before transfer to PD was significantly associated with a higher occurrence of death or retransfer to HD (cs-HR 1.01, 95% CI 1.00-1.02 for 1 month increase). It was linearly modeled, without polynomial transformation being required for the variable time spent in HD.

When considering competing events, time spent on HD before transfer to PD remained associated with the composite endpoint (sd-HR 1.01, 95%CI 1.00-1.02).

PD cessation for death (censored on retransfer to HD)

Time spent on HD before transfer to PD was significantly associated with death censored on retransfer to HD (cs-HR 1.02, 95%CI 1.01-1.03 for 1 month increase) after adjustment for other variables (Figure 3B). Again, it was modeled linearly across all imputed datasets.

Age was strongly associated with death as well as comorbidities such as cardiovascular disease (cs-HR 1.48, 95%CI 1.23-1.78), heart failure (cs-HR 1.33, 95%CI 1.13-1.57), cirrhosis (cs-HR 2.45, 95%CI 1.55-3.89), and cancer (cs-HR 1.38, 95%CI 1.09-1.75). Nurse assistance was associated with death even after adjustment for comorbidities (cs-HR 2.23, 95%CI 1.77-2.82).

Unplanned HD start markers seemed to be associated with death and included the following: emergency HD start (cs-HR 1.21, 95%CI 1.03-1.42) and HD start on catheter (cs-HR 1.23, 95%CI 0.94-1.6).

Cox and Fine and Gray regression models provided similar results.

PD cessation for HD retransfer (censored on death)

Time spent on HD before PD was not associated with retransfer to HD censored on death (cs-HR 1.00, 95%CI 0.99-1.01 for 1 month increase) in the multivariate analysis. Once again, no polynomial transformation was retained.

Diabetes was a risk factor for retransfer to HD (cs-HR 1.38, 95%CI 1.11-1.73), whereas other comorbidities were not associated with this outcome. Age, nurse assistance (cs-HR 0.80, 95%CI 0.66-0.96), and female sex (cs-HR 0.79 95%CI 0.67-0.93) were protective factors for retransfer to HD. Considering competing events did not change these associations. The results are shown in Figure 3C.

All interactions tested on multivariate models across the 3 events of interest were not significant. Notably, the results of Cox model regressions on complete cases and imputed analyses were similar (Supplemental Figure 3).

Discussion

The transition from HD to PD, because of its rare occurrence, remains an understudied event in the integrated management of ESRD. We have shown that the time spent on HD before transfer to PD is associated with an increased risk of PD cessation due to death or retransfer to HD (composite endpoint) and death (retransfer-to-HD censored).

In the few studies describing this transition, time spent on HD before PD is usually considered as a categorical variable divided into early and late transfers. The threshold used to distinguish them is often 3 months. The motivation for the transfer seems to be drastically different depending on its timing. Early transfers may be motivated by the patient's choice in a context of unplanned arrivals, whereas late transfers may result from exhaustion of vascular access, bad tolerance of HD sessions, or by choice (6-12). Our study, by investigating several statistical possibilities of modeling the time spent on HD before transfer to PD, questioned this concept. It appears that linear modeling best described the association between the time spent on HD before transfer and PD outcomes. We can thus assume that the effect of the time spent on HD before transfer on the risk of PD cessation appears from the initiation of HD and increases gradually over time. If a transfer to PD is considered for a patient on HD, it should be prepared and performed as soon as possible after HD initiation to limit the time spent on HD.

Another particularity of our study lies in the fact that all patients transferred from HD to PD were included in our study, regardless of the time spent on HD, while the majority of the previous studies excluded patients staying less than 3 months on HD (6,7,9,10,12). The majority (68%) of our transfers occurred early, within the first 3 months after HD initiation. This result is consistent with the results described by Nessim et al. (14), where the median time on HD before transfer to PD was 83 days. It could reflect a lack of preparation for RRT, since compared to patients remaining on HD, our HD to PD population started HD more frequently in emergency (51% vs 31%) and catheter (85% vs 52%), with a lower use of ESA

at HD initiation (34% vs 40%). Excluding early transfers could have led to a significant underestimation of the incidence of HD-to-PD transfer and its underlying effects. In our opinion, future research should include HD-to-PD transfers regardless of the time spent on HD.

We have shown that the time spent on HD before transfer to PD was associated with an increased risk of death, which could be explained by several reasons. First, one can argue that the transition between dialysis modalities is a period at risk and could have a direct impact on patient survival. In a previous study from our team, unplanned transitions from PD to HD were marked by 100% inpatient admissions and 24% deaths, highlighting the risk of transition periods (5). Although our study did not compare the outcome of PD-first patients versus HD-to-PD patients, the fact that time spent on HD before transfer to PD was linearly associated with PD outcomes suggests not only an effect of the transition but also an effect of the time spent on HD. Second, the fact that the time spent on HD before transfer to PD is associated with an increased risk of death (cs-HR of 1.02, 95%CI 1.01-1.03 for each 1 month spent on HD) could reflect a specific effect of an increased total exposure to RRT. It is acknowledged that time spent on HD is a risk factor for mortality, with a relative risk of death between 1.02 and 1.07 for 1 year spent on HD (22-24). In light of our results, it appears that for each year spent on HD, the increased risk of mortality is even greater for patients transferring to PD than for patients remaining on HD.

Surprisingly, time spent on HD was not associated with retransfer to HD (cs-HR 1.00, 95%CI 0.99-1.01) in our study. When considering the event of transfer, Nessim et al. (14) described a higher risk of PD technique failure for patients transferred from HD to PD compared to patients starting RRT with PD (HR 1.37, 95%CI 1.26-1.49). Similar results have been described in a previous study from our team (15). Residual renal function is modified by time spent on HD and would be an important factor to study in this context (4,25-29).

Unfortunately, we were not able to capture this information in the present study. One could expect that access to kidney transplantation impacts PD survival. We accounted for this hypothesis by considering transplantation as a competing event and performed a Fine and Gray model, which did not change the lack of association observed between time spent on HD before PD and retransfer to HD (sd-HR 0.99, 95%CI 0.98-1.01).

In our study, nurse assistance was significantly associated with a higher risk of mortality but a decreased risk of retransfer to HD, particularly in the population aged over 80. Similar results have been previously described (30-32), and are likely a reflection of increased comorbidity and frailty. One could also expect clinicians to be less likely to suggest a retransfer to HD for frail and dependent patients to favor quality of life on home dialysis.

We also reported a trend toward mortality in cases of unplanned arrival in HD, with cs-HRs 1.21 (95%CI 1.03-1.42) and 1.23 (95%CI 0.94-1.6) for an emergency start and HD start on catheter, respectively. These elements have previously been described (33) and underline the importance of predialysis care.

Our study has some limitations. In the REIN registry, the collection of changes in dialysis modalities of less than 2 months is not exhaustive, which may lead to an underestimation of the number of patients transferred from HD to PD and of the different HRs. Residual renal function was not available in the registry.

In conclusion, this study shows that the transition from HD to PD is a rare event, since only 3% of patients beginning on HD were transferred to PD in our study. This event happens early in the course of RRT, mostly within the first 3 months. Our results appear reassuring in that the median survival time on PD after transitioning was 20 months (IQR 18-21) when considering the composite endpoint (death or retransfer to HD). We found that time spent on HD before transfer to PD impacts patient survival but does not impact retransfer to HD and that the effect of the time spent on HD on the risk of PD cessation seems to increase gradually

over time. We therefore think that it will be interesting to further study the causes of transitioning from HD to PD and the factors associated with better outcomes in that population to identify the patients who would benefit from this strategy.

Disclosures

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Supplemental material

Supplemental Figure 1: Flowchart

Supplemental Figure 2: Survival curve for death or retransfer to HD (composite endpoint) using Kaplan-Meier method

Supplemental Figure 3: Forest plots representing multivariate Cox (imputed) and Cox (complete cases) models for the 3 events of interest

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Tables

Table 1. Patients' characteristics at baseline

Variables	HD to PD patients n = 1985	Patients remaining in HD n = 75133
Age (years), median (IQR)	67.67 (51.92 - 79.69)	71.20 (59.97 - 79.86)
Sex, male, n (%)	1246 (63)	47766 (64)
Underlying nephropathy, n (%)		
Polycystic kidneys	71 (4)	4155 (6)
Diabetic nephropathy	372 (19)	17621 (23)
Glomerulonephritis	292 (15)	7914 (11)
Vascular or hypertensive nephropathy	498 (25)	20142 (27)
Other	395 (20)	14704 (20)
Unknown	357 (18)	10597 (14)
Comorbidities		
BMI (kg/m ²), median (IQR)	24.38 (21.77 - 27.91)	25.59 (22.38 - 29.73)
Missing	390 (20)	16502 (22)
Diabetes, n (%)	709 (36)	32090 (43)
Missing	15 (1)	992 (1)
Cardiovascular disease ^a , n (%)	939 (47)	37164 (49)
Missing	53 (3)	2686 (4)
Congestive heart failure, n (%)	629 (32)	19008 (25)
Missing	40 (2)	2293 (3)
Cancer, n (%)	161 (8)	8695 (12)
Missing	41 (2)	2309 (3)
Chronic respiratory disease, n (%)	206 (10)	11058 (15)
Missing	57 (3)	2806 (4)
Cirrhosis, n (%)	40 (2)	1790 (2)
Missing	43 (2)	2365 (3)
HD characteristics		
Emergency HD start, n (%)	1021 (51)	22996 (31)
Missing	87 (4)	4400 (6)
HD start on catheter, n (%)	1689 (85)	39332 (52)
Missing	68 (3)	2991 (4)
ESA use at HD initiation, n (%)	670 (34)	29855 (40)
Missing	268 (14)	11904 (16)
PD characteristics		
Time spent on HD before PD transfer (months), median (IQR)	1.94 (1.02-4.01)	
PD modality, n (%)		
Automated PD	610 (31)	
Continuous ambulatory PD	1374 (69)	
Missing	1 (0)	
Nurse assistance, n (%)	989 (50)	
Missing	343 (17)	

Values are expressed as median (IQR) or n (%).

^a Includes stroke or transient ischaemic attack, dysrhythmia, peripheral vascular disease, coronary heart disease.

HD, hemodialysis. PD, peritoneal dialysis. BMI, body mass index. ESA, erythropoiesis stimulating agent.

Figure legends

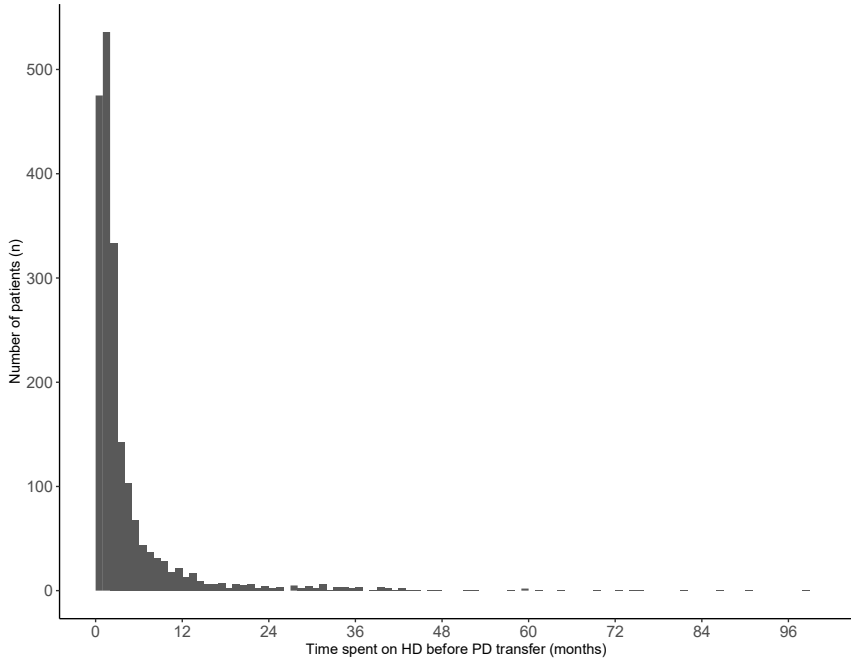


Figure 1: Distribution of time spent on HD before transfer to PD

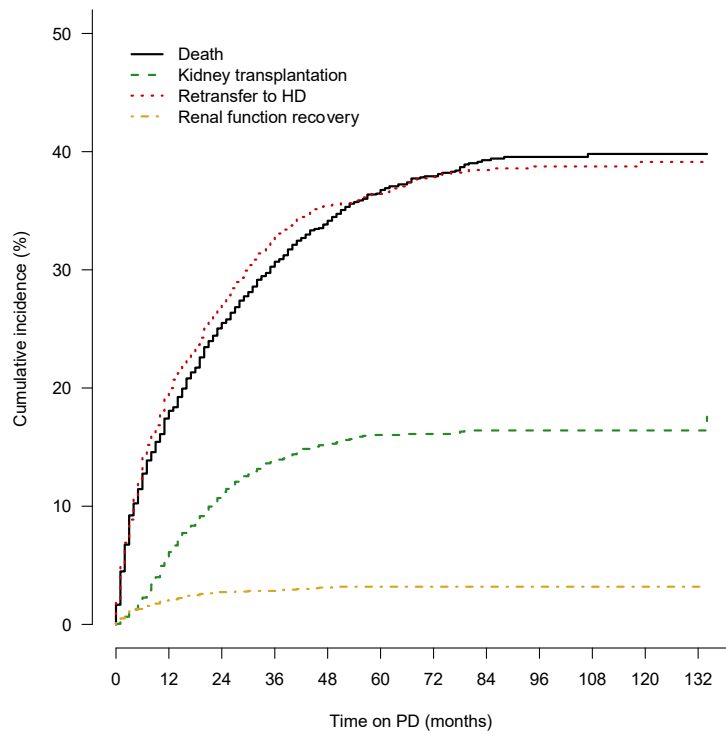


Figure 2: Cumulative incidence functions

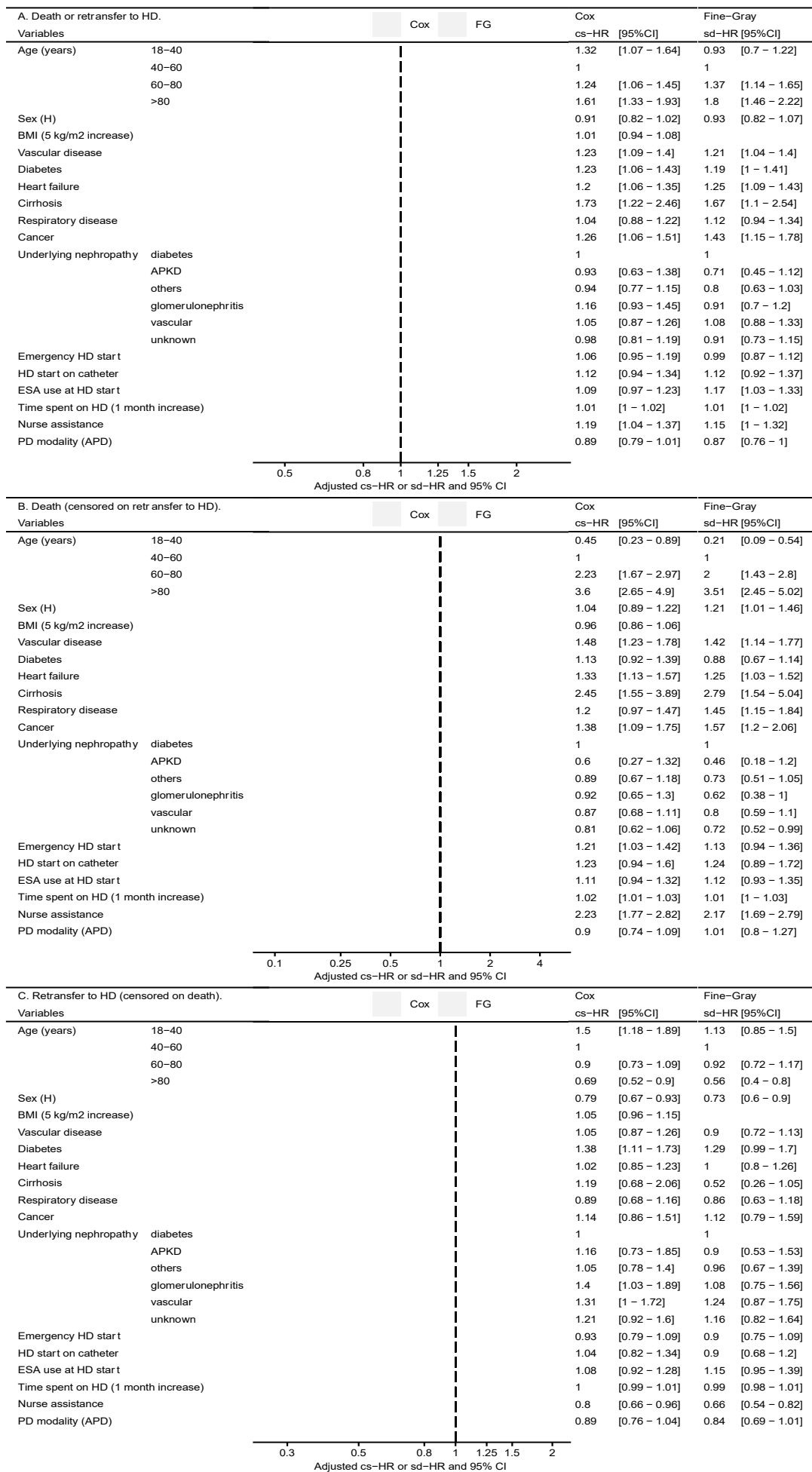


Figure 3: Forest plots representing multivariate Cox and Fine-Gray models for the 3 events of interest: A. Death or retransfer to HD (composite endpoint). B. Death. C. Retransfer to HD.

VII. Discussion

1. Main results

The results of our work are complementary to ongoing research towards a better understanding of PD utilization, in order to increase the efforts to further expand PD access for patients in need of KRT in Europe. The application of our results is notably interesting for elderly and frail patients, a population often denied the possibility of home dialysis.

Firstly, we have investigated the impact of the implementation of an assisted PD service on PD initiation. It could be anticipated that provision of an assisted PD service, by increasing the number of patients eligible to PD notably in the elderly and frail population, would increase PD initiation. However, this had never been clearly demonstrated previously. With the present study, we have reported how the introduction of an assisted PD service positively influenced the uptake of PD and counterbalanced the decline in PD rates over time. However, our study being set in a single centre where a strong motivation on PD exists, our results might not be fully generalizable to other settings. Indeed, it is likely that a centre experiencing difficulties with PD utilisation will not be successful in implementing an assisted PD programme. Furthermore, the reimbursement system surely impacts the implementation of assisted PD programmes. In countries where reimbursement by the healthcare system is absent or insufficient for the cost of assistance, it would be difficult to implement it as neither the patient nor the dialysis unit would be willing to pay for the additional costs.

Therefore, in the second part of our work, we aimed at describing assisted PD utilization over the past decade. In France, assistance can be provided either by a family member (family-assisted PD) or a nurse (nurse-assisted PD), and is fully covered by the healthcare system. With the CKD population growing older and frailer, an increase in assisted PD utilization over time would be anticipated. However, our results showed a different pattern:

there was in France a constant and linear decline of family-assisted PD, which has led to a decrease in assisted PD utilization until 2013. The secondary rise in assisted PD utilization, observed since 2013, is mainly the result of an increase in nurse-assisted PD utilization, which could be explained by economic incentives introduced in 2011 to increase PD utilization for ESKD patients in nursing homes. Our results show that, due to a decline in family assistance, assisted PD currently relies on nurse assistance. As previously described economic incentives seem to be effective at increasing the use of home dialysis (115). The implications of our results are that economic strategies promoting nurse-assisted PD, by increasing its utilization and thus providing PD as an option for the frail and elderly patients, would increase the population eligible to PD and secondarily translate in an increase of PD initiation (129). However, the impact of assistance on PD prevalence remains unknown even though assistance has been associated with a lower risk of technique failure, but a higher risk of death as the patients are older and frailer (114).

Therefore, we have pursued our research and studied the evolution of PD technique survival (death or transfer to HD), transfer to HD and the individual causes of transfer to HD, and patient survival over the past decade in France. We have shown that both PD cessation (due to either death or transfer to HD) and death linearly declined over time, without any differences in whether the patients were autonomous or assisted, and that transfer to HD declined from 2011 particularly in self-PD patients. The decline in transfer to HD rates observed since 2011 is mainly due to a significant decline in infection-related transfers, which was not observed in assisted PD patients.

Finally, the last part of the thesis demonstrated that the transition from HD to PD is a rare event, often understudied, mostly happening early in the course of KRT. Time spent on HD before transfer to PD impacts patient survival but does not impact retransfer to HD, and

importantly the effect of the time spent on HD on the risk of PD cessation seems to increase gradually over time. Transfer is traditionally divided in early and late transfer, the arbitrary threshold used to distinguish them being 3 months. The motivation for the transfer seems to be drastically different depending on its timing. Early transfers may be motivated by the patient's choice in a context of unplanned arrivals, whereas late transfers may result from exhaustion of vascular access, bad tolerance of HD sessions, or by choice. We therefore think that it will be interesting to further study the threshold that better divides the two timings of transfer; and study the causes of transitioning from HD to PD and the factors associated with better outcomes in that population to identify the patients who would benefit from this strategy.

2. Perspectives

After completing this thesis, some interrogations remain regarding PD utilization. PD technique failure should be further analysed, notably to better understand the impact of medical programs such as assistance on PD prevalence. Elderly ESKD patients are still often deprived from a shared decision-making regarding their treatment modality, as they are usually not offered the possibility of home dialysis and kidney transplantation. Future studies should focus on investigating strategies towards a free choice for all.

A. PD technique failure

Trends in causative organisms of peritonitis over time

In our work, we have described a decline in infection-related transfers to HD, which seems to be consistent worldwide (84–86,170,171) and could be explained by the development of educational programs (127,141–147), as well as international changes in

medical practices; notably the use of twin bag disconnection systems and topical exit-site antibiotics (136,139,153,154,172,173). All of these measures should decrease peritonitis caused by contamination with skin organisms during connection procedures, mainly cocci gram positive peritonitis.

Only few studies in the literature describe the temporal trends in peritonitis' microbiological findings (172,174). A retrospective observational cohort study of a single PD-centre in Korea reported a significant improvement in peritonitis rates, occurring primarily in gram positive peritonitis, whereas gram negative peritonitis rates remained constant (174). Similar findings have been described in Taiwan (175). But this decline in cocci gram negative peritonitis rates over time is not that evident. Rocha *et al*, described a global peritonitis reduction over time, yet no significant change of the causative organisms was observed (176), while a significant increase in gram-negative organism over time has been described in Turkey (140). Of note, all of these were single centre studies and most of them included a small number of patients.

We would like to investigate the temporal trends in peritonitis' causative organisms over time in France, in order to assess the impact of preventive measures on contamination with skin organisms. Using the data from the RDPLF, we will explore the association between calendar time and the different peritonitis' causative organism, using a Cox regression model with robust variance to estimate the PR and their 95% CI. We are expecting to describe a decline in gram-positive peritonitis over time, which would emphasize the effectiveness of education and preventive measures on peritonitis caused by contamination with skin organisms.

Estimation of the baseline hazard of PD cessation and peritonitis according to the assistance status

Modelling of censored survival data by medical researchers is almost always done by using Cox proportional hazards regression, due to its ease of calculating the relative effects of hazards between groups without needing to estimate the baseline hazard function. In the Cox regression, the hazard function of an outcome of interest according to an explanatory variable (x) for individual i can be written as:

$$h_i(t) = e^{\beta x_i} * h_0(t)$$

where x takes the value of the explanatory variable for individual i and h_0 is the baseline hazard.

The baseline hazard is treated as a nuisance parameter, so the partial likelihood is maximized, which enables estimation of the regression parameters, but not the baseline hazard function which is considered constant over time assuming proportional hazards. As a result, absolute measures of the hazard rates can only be estimated at the event times, resulting in a step function where the estimate at one event is held constant and carried forward until the time of the next event (89,169,177).

The assumption of proportional hazards is often unreasonable in epidemiological studies. It is of importance to understand the changing effect of a covariate over the time-course of an illness rather than assuming a constant hazard. Understanding the behaviour of the baseline hazard function may help to elucidate the natural history of the disease and to reveal time-related effects of treatment. For example, incidence rate of PD cessation is highest during the first 3 months after initiation, and then remains stable (130,150). The importance of early dropout from PD, notably because of catheter related issue which will manifest early on in the follow-up, is acknowledged, but this effect secondly decreases as time goes on. After

the first months on PD, reasons of transfer to HD are mostly represented by infectious complications and inadequate dialysis (130,150). This illustrates that the baseline hazard of PD cessation is probably not constant over the time-course on PD, an important information that is not well captured when using Cox proportional hazards regression. Assistance has been associated with a lower risk of technique failure (114,170) and particularly of transfer to HD due to inadequate dialysis (170). Nurse assistance has also been associated with a lower risk of infection in diabetic and elderly patients (63,178,179). As the reasons of transfer to HD are different at various points of follow-up, one could speculate that the protective effect of assistance on PD survival and peritonitis is not constant over time. However, this has never been demonstrated before.

The Royston model, a flexible parametric model described in 2002, by fitting a restricted cubic spline which permits estimation of a continuous function instead of a step function, appears to offer adequate flexibility for approximating the baseline distribution function (169). This feature enables absolute measures of effect to be estimated at all time points, and incorporates time-dependent effects. By using a Royston model, we will be able to investigate the baseline hazard of PD technique survival and peritonitis, according to the assistance status (self-PD patients versus assisted-PD patients).

B. Trends in registration rates on the transplant waiting list of incident dialysed patients aged over 70 years over the past decade

The incidence of ESKD is increasing most rapidly in people aged 65 years and older. In 2018, the median age at KRT initiation in France was 70,4 years (4). Age *per se* is not considered as a contra-indication to kidney transplantation. Nonetheless, in 2012 in France

the median age of kidney transplanted patient was 49 years, with less than 9.7% of performed kidney transplants allocated to patients aged over 70 years (78).

In Europe, access to kidney transplantation for older dialysed patients increased from 0.3% in 2005 to 0.9% in 2014, with a wide variation across European countries. The majority of allografts allocated in patients aged over 75 years are from old deceased donors. The use of extended criteria donors (all donors aged over 60 years) could partly explain this increase (180). A trend towards improved patient and graft survival in older kidney transplant recipients has been described over the past decade in the literature (180,181). Despite these encouraging results, in the French and European dialysis population aged over 70 years access to kidney transplantation remains low and allocation of kidney transplants a rare event.

In the latest national HAS recommendation on kidney transplantation, “Transplantation rénale - accès à la liste d’attente nationale” published in 2015, it is now recommended to start a pre-transplant investigation up to 85 years in the absence of another contraindication to kidney transplantation. An evaluation of life expectancy by a validated tool is also suggested (182). This latest recommendation, by expanding the age criteria, contrasts with previous transplant practices which limited access to kidney transplant for older dialysed patients.

In order to explore the impact of these recommendations on the registration rates, we have submitted an expression of interest to the REIN registry to conduct a study aiming at describing trends in registration rates on the kidney transplant waiting list of incident dialysed patients aged over 70 years, and assessing the impact of the recommendations published in 2015 to promote kidney transplantation for the elderly patient. We will include patients aged over 70 years, incident on KRT between January, 1st 2010 and December, 31th 2019, registered in the REIN registry. We believe that the registration rates on the transplant waiting list of

elderly patients increased over time, and notably since the latest recommendations. Data will be analysed with a Poisson regression, the event of interest being the registration on the transplant waiting list. The Poisson regression will enable us to describe the instantaneous speed of occurrence of the event, and to account for the time-dependent exposition to the recommendations (102). Secondly, we will estimate the registration on the transplant waiting list's prevalence ratios using a Cox regression with robust variance (103), accounting for the non-linear impact of time with regression splines and FPs. Analyses will be adjusted for patients' comorbidities.

C. Home dialysis implementation, an international comparison

There is a wide variation in home dialysis usage across the world. Up to 50% of dialysed patients dialyse at home in New-Zealand. This proportion falls to 30% in Australia, 20% in Canada, 19% in the UK and 7% in France (4,27,77,183). Several reasons could explain this variation between countries in home dialysis usage, notably national-level factors such as the medical strategy used (Eg PD first policy) and healthcare system. One could also expect a part of variability to be explained by centre- and patient-level characteristics (113,139,184–187).

To date, most of the studies are based on national registries, providing information on a regional and national level. By using patient level data from multiple countries combined in one study, we could better understand the reasons for described differences in home dialysis usage and allow more accurate estimates of relative differences.

We are currently working on an international research project that will describe home dialysis usage in the UK, France, Canada, Australia, New-Zealand and United State of America (USA). We will work in collaboration, using the data from the following national registries: Dr

Mark Lambie and Pr Simon Davies for the UK Renal Registry (UKRR), Pr Thierry Lobbedez, Dr Clémence Béchade and myself for the REIN registry, Dr Annie-Claire Nadeau-Fredette and Dr Karthik Tennankore for the Canadian Organ Replacement Registry (CORR), Pr David Johnson for the Australian and New-Zealand Dialysis and Transplant Registry (ANZDATA), and Dr Wienhandl US renal Data System (USRDS). Analyses will be carried out, as much as possible, in an identical way by each registry (data won't be linked between the registries), to describe overall home dialysis rates across participating registries and how these vary across registries.

For each country, we will detail the incidence of home dialysis (peritoneal and haemodialysis), as well as the population on these modalities and the different approaches to its provision (health care and reimbursement system). We will also describe the temporal trends of home dialysis usage over time in each country. The study will include a description of the impact of differences in patient characteristics and transplantation rates on home dialysis usage, thereby providing a better estimate of the magnitude of the impact of other drivers of home dialysis usage, such as culture, remuneration practices and differences in healthcare systems. Variables describing patient-level and centre-level data will be used to describe home dialysis usage in each country. Firstly, we will describe for each country, and each home dialysis modality (PD and HHD) a description of the population, the yearly incidence rates using an interval Poisson regression adjusted on age and comorbidities and an overview of the health care and reimbursement system of the country. The second part of the analysis will use a Cox model with robust variance to estimate the prevalence ratio of home dialysis, enabling us to describe the temporal trends of home dialysis usage over time in each country.

The use of patient-level data from several countries will enable us to investigate the differences in home dialysis implementation, which could be linked to differences in healthcare and reimbursement systems.

D. Transfer from HD to PD

Transfer from HD to PD remains a rare and understudied event. The traditional 3 months threshold to differentiate early and late transfers, which appear to have drastically different motivations, is arbitrary and has never been investigated. A Royston approach, with a joint-point regression, could enable us to better define the cut-off timing that best divides early and late transfers. In addition, in the last part of our work, the median survival time on PD after transitioning was 20 months when considering the composite endpoint (death or retransfer to HD), which is reassuring. It would be interesting to further study the causes of transitioning from HD to PD, notably in case of late transfers, and the factors associated with better outcomes in that population to identify the patients who would benefit most from this strategy.

E. Investing strategies towards a free choice for all

Patients should be offered a free choice regarding their treatment modality. In this sense, it could be interesting to develop qualitative studies in order to better understand the reasons driving patients and healthcare professionals towards the choice of home dialysis. By better understanding these motivations and drivers, ideas of incentives to further develop home dialysis could arise.

3. Conclusion

In the interest of shared decision-making, patients should be offered a free choice regarding their treatment modality, which implies that all modalities are available and can be chosen. It is thus necessary for centres not only to offer PD, but also to offer it in all its different modalities. A broad implementation of assisted PD, by increasing the range of available options, will allow more people to choose the option that best fits their preferences and expectations, particularly for the frail and elderly patient. Several reasons could explain why PD uptake remains low in Europe, with interconnection between these barriers (188).

One could reasonably think that a single intervention will not be sufficient for change. However, in lights of the results of this work, we believe that economic incentives promoting the reimbursement of assisted PD added with a shift in mentality and an increased commitment to PD could successfully increase PD rates and enable patients to have a free choice regarding their treatment modality.

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Communications in the course of the thesis

“Impact of the implementation of an assisted peritoneal dialysis service on peritoneal dialysis initiation”

BOYER A., SOLIS-TRAPALA I., TABINOR M., DAVIS S., LAMBIE M.

14th European peritoneal dialysis meeting; may 2019; Ljubljana; Poster.

“Impact of the implementation of an assisted peritoneal dialysis service on peritoneal dialysis initiation”

BOYER A., SOLIS-TRAPALA I., TABINOR M., DAVIS S., LAMBIE M.

5th congress of the Société Francophone de Néphrologie, Dialyse et Transplantation; October 2020; Poster.

“Trends in assisted peritoneal dialysis over the last decade: a cohort study from the RDPLF”

BOYER A., LANOT A., LAMBIE M., GUILLOUET S., LOBBEDEV T., BECHADE C.

5th congress of the Société Francophone de Néphrologie, Dialyse et Transplantation; October 2020 ; online congress. Oral communication.

“Trends in Peritoneal Dialysis Technique Survival, Death, and Transfer to Haemodialysis: A Decade of Data from the RDPLF”

BOYER A., LANOT A., LAMBIE M., VERGER C., GUILLOUET S., LOBBEDEV T., BECHADE C.

6th congress of the Société Francophone de Néphrologie, Dialyse et Transplantation; October 2021 ; Toulouse. Oral communication.

Collaborations outside of the course of the thesis linked with the thematic area

- Assisted peritoneal dialysis

In France, where assisted PD has been available for many years, selection of patients for assistance is based on the nurse's assessment of the patient's ability to be on self-care PD and on the nurse's evaluation of the patient's ability to handle the PD devices. If the nurse's assessment is that the patient cannot have self-PD, the patient can choose to be assisted by a relative or a nurse. To date, neither the patient nor the caregiver is assessed with tools that have been validated in the field of PD for the evaluation of his ability to perform PD. Our team conducted several studies exploring the association between the nurse's subjective assessment of the patient's ability to perform PD and evaluating tools that assess the patient's ability to manipulate PD devices.

* Assessment for assisted peritoneal dialysis by peritoneal dialysis nurses: results of a cohort study. GUILLOUET S., **BOYER A.**, LANOT A., FICHEUX M., LOBBEDEV T., BECHADE C. American Journal of Nephrology. 2019, 50(6):489-498.

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- * Percutaneous Ablation of hepatocellular carcinoma and Peritoneal Dialysis. **BOYER A.**, JEGONDAY MA., LANOT A., FICHEUX M., LOBBEDEV T., BECHADE C. Peritoneal Dialysis International; 2017,37(6):656-658.
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Résumé en français

Introduction Générale

1. L'insuffisance rénale chronique terminale

L'insuffisance rénale chronique (IRC) se caractérise par une diminution progressive et irréversible du débit de filtration glomérulaire (DFG) et/ou la présence d'un marqueur d'atteinte rénale depuis plus de trois mois. Les méthodes de mesure directe du DFG étant complexes (clairance de l'inuline, méthode isotopique...), il est recommandé d'estimer la fonction rénale à partir d'équations prenant en compte le dosage de la créatinine sérique et de certains facteurs tels que l'âge, le sexe, le poids et l'ethnie. L'insuffisance rénale chronique terminale (IRCT) est définie selon les KDIGO et l'HAS par la persistance d'un DFG inférieur à $15\text{mL/in}/1,73\text{m}^2$ ou par l'existence d'un traitement de suppléance rénale.

Au sein du traitement de suppléance rénale se différencient l'épuration extra-rénale et la transplantation rénale. Pour les patients en IRCT, la transplantation rénale est associée à une meilleure survie et qualité de vie. Cependant tous les patients ne sont pas éligibles à une transplantation rénale. Par ailleurs, plusieurs modalités d'épuration extra-rénale existent, certaines étant réalisées dans une structure de soins et d'autres au domicile du patient. La dialyse hospitalière est représentée par l'hémodialyse en centre (HD) alors que la dialyse à domicile comprend la dialyse péritonéale (DP) et l'hémodialyse à domicile (HDD). Aucune étude n'a permis de démontrer la supériorité d'une modalité de dialyse par rapport aux autres. Une autre stratégie de la prise en charge de l'IRCT est le traitement conservateur, qui se définit comme une prise en charge néphrologique active sans recours à la suppléance rénale. Cette stratégie a pour objectif de diminuer le risque de survenue de complications en lien avec la maladie rénale, à traiter les symptômes décrits par le patient et à introduire des soins de support sans débiter un traitement de suppléance rénale.

L'incidence et la prévalence de l'IRCT sont inconnues. En revanche, si le nombre de patients qui reçoivent un traitement de suppléance rénale est bien estimé grâce aux registres nationaux, celui des patients qui atteignent l'IRCT mais sans traitement de suppléance reste inconnu. L'épidémiologie de l'IRCT est donc majoritairement reflétée par l'épidémiologie du traitement de suppléance rénale. Selon le Réseau Epidémiologique en Néphrologie (REIN), en France en 2018, 10879 patients ont commencé un traitement par dialyse et 464 ont reçu une transplantation rénale en premier traitement de suppléance rénale, soit une incidence globale de l'IRCT traitée par suppléance rénale de 168 par million d'habitants.

L'incidence de l'IRCT augmente rapidement dans la population âgée de plus de 65 ans. Cette population est à risque de développer des complications liées à l'âge telles que des chutes, de la dénutrition, une démence ; le tout entraînant une perte d'autonomie. Tous ces facteurs impactent la prise en charge de la maladie rénale. En effet, la majorité des patients âgés de plus de 65 ans présentent de nombreuses comorbidités, contre-indiquant l'accès à la transplantation rénale, leur laissant comme possibilité de traitement le choix entre la dialyse ou le traitement conservateur. Un déclin des capacités fonctionnelles dans les 6 mois suivant l'initiation de la dialyse a été observé chez une grande proportion des patients âgés. Étant donné la perte d'autonomie fréquente dans cette population, l'hémodialyse en centre leur est majoritairement proposée, puisque les fragilités liées à l'âge peuvent présenter des obstacles à la réalisation de la dialyse à domicile. Cependant, en limitant les transports jusqu'au centre de dialyse et en étant réalisée à domicile, la dialyse péritonéale a l'avantage de préserver une certaine autonomie et qualité de vie chez le sujet âgé.

2. La place de la dialyse péritonéale dans la prise en charge de l'insuffisance rénale chronique terminale

Le traitement par dialyse péritonéale a été associé à une meilleure qualité de vie, une meilleure préservation de la fonction rénale résiduelle, une survie similaire et un moindre coût que l'hémodialyse intra-hospitalière. Cette modalité de dialyse permet au patient de préserver un certain degré d'autonomie. Par ailleurs, elle limite les transports jusqu'au centre de dialyse, les difficultés de création d'abord vasculaire ainsi que l'instabilité hémodynamique parfois observée lors des séances d'hémodialyse.

Malgré ces avantages, il existe de nombreux obstacles à l'utilisation de la DP, tel que l'âge, le manque d'autonomie, les comorbidités et l'isolement social. En conséquence, peu de sujets âgés ont la possibilité de réaliser leur dialyse seul au domicile. Dans certains cas un membre de la famille peut assister le patient.

Dans certains pays, la mise en place de programme d'assistance, par une infirmière ou un membre de la famille entraîné à la réalisation de la DP, permet de surmonter ces obstacles et d'améliorer l'accessibilité de la DP aux sujets âgés. Les premiers programmes d'assistance sont apparus dans les années 1980 en France. Les frais liés au passage d'une infirmière libérale au domicile du patient, ou dans un EHPAD, pour la réalisation des séances de dialyse péritonéale sont pris en charge par la sécurité sociale jusqu'à quatre passages par jour. Selon les données du Registre de Dialyse Péritonéale de Langue Française (RDPLF), 50% des patients incidents en DP entre 1995 et 2006 étaient considérés dépendant pour la réalisation des séances de dialyse et requéraient de la DP assistée. Dans la population des sujets âgés, plus de 80% avaient besoin d'une assistance.

L'utilisation de la DP est en déclin depuis plusieurs années, alors que le nombre total de patient dialysé augmente. Entre 1997 et 2008, la proportion de patients dialysés traités par dialyse péritonéale a diminué de 5.3% dans les pays développés. De plus, on observe une grande disparité d'utilisation de la DP à l'échelle de la France. Plusieurs raisons peuvent

expliquer la sous-utilisation de cette modalité de dialyse. Premièrement, l'initiation de la DP reste insuffisante, telle que l'indique l'incidence décroissante au cours des dernières années. Il est possible que ce déclin soit lié au vieillissement de la population, qui pourrait limiter l'utilisation de modalité de dialyse à domicile en l'absence d'assistance. Cependant les données actuelles disponibles dans la littérature ne permettent pas de confirmer cette hypothèse. De plus, des stratégies visant à promouvoir la dialyse à domicile, telle que la DP assistée, ont été déployées dans de nombreux pays. On peut supposer que la mise en place de programmes de DP assistée, en surmontant certains obstacles à la dialyse à domicile, augmente le nombre de patients éligibles à la DP et donc le nombre de patients initiant cette modalité de dialyse. Des incitations financières favorisant le remboursement de l'assistance dans les EHPADs ont également été introduites en France récemment, mais l'impact de ces incitations reste à ce jour inconnu. Un autre facteur limitant l'utilisation de la DP est la survie de la technique. En effet, le nombre de transferts en HD pourrait expliquer la faible prévalence de la DP. Même si des améliorations des taux de péritonites ont été observés ces dernières années, il n'existe que peu de données sur les tendances temporelles de survie de la technique de DP au cours des dernières décennies. Finalement, il est désormais admis que les patients expérimenteront plusieurs transferts entre les différentes modalités de dialyse au cours de leurs parcours. Cependant les données concernant les transferts de l'HD vers la DP sont rares, or on peut supposer que le temps passé en HD avant un transfert vers la DP impacte le devenir en DP.

Dans ce travail, nous combinerons les données de patients en DP de France et au Royaume-Uni, afin de répondre à certaines lacunes dans les connaissances actuelles sur la sous-utilisation de la DP.

3. Particularités méthodologiques

Lorsqu'une variable est introduite dans un modèle de survie, la valeur de cette variable est habituellement celle renseignée au début de l'étude, ce qui ne reflète pas toujours la réalité. En effet, l'exposition à un facteur de risque peut évoluer au cours de la durée de l'étude, auquel cas cette variable sera dépendante du temps. Il est important de bien définir ce type de variable, afin de pouvoir la prendre en compte. En cas d'analyse avec une variable dépendante du temps, le suivi des patients est divisé en différents intervalles de temps, et la valeur de la variable dépendante du temps est alors renseignée au début de chaque intervalle. Une analyse de Cox est réalisée pour chaque intervalle de temps modélisant la valeur de la variable enregistrée. Secondairement, une moyenne pondérée de tous les résultats des différents intervalles de temps est calculée, correspondant aux résultats finaux.

L'analyse entre un événement d'intérêt et une variable continue suppose classiquement que leur relation est linéaire. En cas de non-linéarité, il est préférable de transformer cette variable pour l'analyse. Habituellement, une transformation en différentes catégories est réalisée, ce qui implique de définir les limites des catégories et entraîne une perte d'information. Une autre possibilité est la transformation en polynômes fractionnels. Le polynôme fractionnel prend la forme $\beta_1 X^p$, x étant la variable, β_1 le coefficient et p la puissance du polynôme. Le polynôme est communément choisi entre $\{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}$, par convention X^0 étant $\ln(X)$. La modélisation de variables explicatives en polynômes fractionnels permet une grande flexibilité et s'ajuste au plus proche des valeurs de cette variable.

Lorsque l'évènement d'intérêt d'une étude de survie est fréquent, l'odds ratio (OR) peut surestimer le prévalence ratio (PR). Plusieurs alternatives à l'utilisation de l'OR ont été décrites dans la littérature, notamment par l'utilisation de modèle estimant directement le PR. Un

modèle de Cox à variance robuste ou une régression de Poisson sont deux alternatives qui permettent de donner des estimations fiables du PR et de son intervalle de confiance à 95% (IC 95%).

Dans le cadre de ce travail, des modèles de Cox à variance robuste avec si besoin des modélisations par polynômes fractionnels et variables dépendantes du temps, ont été réalisés afin de décrire l'évolution au cours des dernières décennies de l'utilisation et de la survie en DP.

Impact de la mise en place d'un programme de dialyse péritonéale assistée sur l'initiation de la dialyse péritonéale

1. Introduction

Malgré les avantages que présente la dialyse péritonéale, l'utilisation de cette modalité de dialyse est en diminution depuis plusieurs années. Une des raisons expliquant cette diminution pourrait être le vieillissement de la population, avec une augmentation des conditions sociales et médicales chez les sujets âgés qui limitent la réalisation de la dialyse à domicile sans l'aide d'une assistance. La mise en place de programmes de DP assistée permet d'augmenter le nombre de patients éligibles à la DP, cependant l'impact de ces programmes sur l'initiation de la DP reste à ce jour inconnu. L'objectif de cette étude était d'estimer l'impact de la mise en place d'un programme d'assistance en 2011 dans un centre de dialyse au Royaume-Uni sur l'initiation de la DP.

2. Matériels et méthodes

Les données des patients inscrits dans la base de données du service de néphrologie du Royal Stoke University Hospital ont été utilisées pour cette étude. L'évènement d'intérêt principal était l'initiation de la DP chez les patients incidents en épuration extra-rénale (EER). Le facteur d'exposition principal était la disponibilité du programme de DP assistée, mis en place en 2011, les autres variables étant les comorbidités et le temps jusqu'à l'initiation de l'EER (soit le temps entre le début de la période d'observation de l'étude et la date de début d'EER).

La disponibilité du programme de DP assistée variant en fonction de la date de début d'EER (avant ou après 2011), nous avons utilisé pour cette étude une analyse de Cox en modélisant le programme de DP assistée par une variable dépendante du temps. L'impact non linéaire du temps a été exploré par des splines, avec une transformation en polynômes fractionnels ou en catégories lorsque nécessaire. Les évènements de décès et de transplantation pouvant impacter l'incidence cumulative de l'initiation de la DP, ces évènements ont été considérés comme des évènements compétitifs et modélisés par une régression de Fine and Gray.

Les données étant manquantes pour plusieurs variables, avec plus de 10% de données manquantes pour deux variables, une imputation multiple par équation chaînée a été réalisée.

3. Résultats

Entre janvier 2002 et 2017, 1576 patients incidents en EER ont été inclus dans l'étude, parmi lesquels 1126 (71%) ont débuté l'EER par de l'HD, 370 (24%) par de la DP et 80 (5%) par une transplantation préemptive.

La disponibilité du programme de DP assistée était associée à une augmentation du taux d'initiation de DP (cause-specific hazard ratio (cs-HR) 1.78, IC 95% 1.21-2.61). Une diminution

de l'initiation de la DP sur la première partie de l'étude était observée, avec une stabilisation de ce déclin à partir de 2010.

Les taux de transplantations et de décès ont augmenté au cours de l'étude, sans affecter les taux d'initiation de DP.

4. Discussion

Cette étude a permis de donner une première description de l'impact de la mise en place d'un programme de DP assistée sur l'utilisation de la DP, dans un centre au Royaume-Uni. Nous avons observé une augmentation d'approximativement 80% d'initiation de DP suite à la mise en place du programme d'assistance, limitant la diminution du taux de DP au cours du temps. Ces résultats semblent indépendants des événements compétitifs.

Un autre résultat important est que l'impact positif observé sur l'initiation de la DP n'a été perçu qu'à partir d'un ou deux ans après la mise en place du programme d'assistance. Ce résultat est important à transmettre aux praticiens souhaitant mettre en place un programme d'assistance, puisqu'il est nécessaire de persévérer et de monitorer le programme avant de percevoir ses effets bénéfiques.

L'implication des résultats de notre étude est que le déploiement à grande échelle de programme de DP assistée pourrait permettre d'augmenter significativement les taux d'initiation de la DP, notamment en rendant accessible la DP aux sujets âgés. Cependant nos résultats ne permettent pas d'interpréter l'impact de l'assistance sur la prévalence de la DP. La DP assistée a été associée à un moindre risque d'échec de technique ou de transplantation, mais un risque plus important de décès puisque les patients sont plus âgés et comorbides. Il est donc possible que l'utilisation à grande échelle de la DP assistée permette d'augmenter la prévalence de la DP.

Cette première étude nous a permis de souligner l'importance de l'utilisation de programme de DP assistée. Nos résultats pourraient être un argument afin de mettre en place des incitations économiques visant à promouvoir la DP assistée. Certains pays, tels que la France, ont introduit récemment des stratégies économiques promulguant la dialyse à domicile. Cependant, il n'existe que peu de données dans la littérature sur l'impact de ces stratégies économiques.

Tendance d'utilisation de la dialyse péritonéale assistée au cours de la dernière décennie : une étude de cohorte

1. Introduction

Les variations d'utilisation de la DP assistée au cours du temps n'ont été que peu étudiées dans la littérature. En France, des incitations économiques ont été mises en place afin de promouvoir l'utilisation de la dialyse à domicile, notamment en 2011 avec le remboursement de la DP assistée par des infirmiers libéraux pour les patients résidents en EHPAD.

L'objectif de cette deuxième étude était de décrire les tendances d'utilisation de la DP assistée selon le type d'assistance (infirmière ou membre de la famille), et d'évaluer si la mise en place d'incitations économiques en 2011 en France est associée à une augmentation de l'utilisation de la DP assistée par infirmière.

2. Matériels et méthodes

Pour cette partie de l'analyse nous avons réalisé une étude rétrospective, multicentrique, basée sur les données du RDPLF, portant sur 11987 patients ayant débuté la DP en France entre le 1^{er} janvier 2006 et le 31 décembre 2015. Un modèle de Cox à variance robuste a été utilisé pour analyser la proportion de DP assistée, par infirmière et par famille, en prenant en

compte l'effet non linéaire du temps par une modélisation en spline et transformation de la variable lorsque nécessaire.

3. Résultats

Sur la période d'étude, 6149 (51%) ont débuté de la DP assistée, 5052 (82%) en DP assistée par une infirmière et 1097 (18%) en DP assistée par un membre de la famille. En analyse multivariée, l'année d'initiation de la DP était associée à la proportion de patients en DP assistée : diminution initiale de l'utilisation de l'assistance de 2008 à 2013 avant une stabilisation, puis une augmentation à partir de 2014. L'utilisation de la DP assistée par infirmière a significativement augmenté après 2012, alors que l'utilisation de la DP assistée par un membre de la famille a diminué de façon linéaire au cours du temps (PR 0.94, IC 95% 0.92-0.97).

4. Discussion

La proportion de DP assistée a diminué jusqu'en 2013, principalement en raison du déclin de l'assistance familiale. Le déclin linéaire de l'assistance par un membre de la famille peut être expliqué par plusieurs raisons. Premièrement, une modification de l'état de santé des aidants a été observée au cours de la période de l'étude, les aidants souffrant de plus en plus de maladie chronique. Par ailleurs, on observe également une augmentation constante de l'isolement social des sujets âgés en France depuis plusieurs années.

L'augmentation de la DP assistée par infirmière observée à partir de 2013 reflète l'impact d'incitations économiques mises en place fin 2011 afin de promouvoir la dialyse à domicile.

Nos résultats montrent qu'en raison d'une diminution de l'assistance par un membre de la famille, la DP assistée repose principalement sur l'assistance par infirmière aujourd'hui. Au

vu de nos résultats précédents, nous soulignons ici l'importance de promouvoir la DP assistée, notamment par des incitations économiques.

Tendances temporelles en dialyse péritonéale sur la dernière décennie : survie technique, transfert en hémodialyse et survie patient

1. Introduction

Une des limitations au développement de la DP est la survie de la technique, qui reste un sujet de préoccupation majeur pour les patients et les soignants. L'arrêt de la DP pour un transfert en HD, pour des raisons infectieuses, d'inadéquation de dialyse ou dysfonction de cathéter, est une limite de l'utilisation de la DP et pourrait en partie expliquer la faible prévalence de la DP.

Certaines caractéristiques des patients et des centres sont associées au risque de transfert en HD. La DP assistée a notamment été associée à un moindre risque de transfert en HD. Depuis 2010, on observe une diminution du taux de péritonites et une diminution du taux de transfert en HD pour cause infectieuse. Cependant les variations de survie en dialyse péritonéale au cours du temps n'ont été que peu étudiées.

L'objectif de cette étude était d'estimer les tendances temporelles d'arrêt de la dialyse péritonéale (pour cause de décès ou transfert en HD), de transfert en HD (ainsi que les causes individuelles de transfert) et de survie patient, au cours de la dernière décennie.

2. Matériels et méthodes

Nous avons réalisé une étude rétrospective, multicentrique, basée sur les données du RDPLF ; portant sur 14 673 patients ayant débuté la dialyse péritonéale en France entre le 1^{er} janvier 2005 et le 31 décembre 2016. Un modèle de Cox à variance robuste a été utilisé pour

analyser la proportion du critère composite de décès ou transfert en HD, de transfert en HD et de décès, en prenant en compte l'effet non linéaire du temps par une modélisation en spline et une transformation de la variable lorsque nécessaire. Parmi les patients transférés en HD, nous avons étudié les causes individuelles de transfert : infection, dialyse inadéquate, dysfonction de cathéter, raison sociale et autres raisons.

3. Résultats

Sur la période d'étude, 10201 (69.5%) patients ont arrêté la DP : 5495 (37.4%) décès et 4706 (32.1%) transferts en HD. En analyse multivariée, la proportion d'échec de DP due à un décès ou un transfert en HD a diminué de façon linéaire au cours du temps (PR 0.96, IC 95% 0.95-0.97). En comparaison à la période 2009-2010, l'initiation de la DP entre 2005-2008 ou 2011-2016 était fortement associée à une moindre proportion de transfert en HD (PR 0.88, IC 95% 0.81-0.96, and PR 0.91, IC 95% 0.84-0.99 respectivement), principalement via une diminution du risque de transfert en HD pour cause infectieuse (PR 0.96, IC 95% 0.94-0.98).

4. Discussion

Nos résultats montrent que les proportions d'arrêt de la DP (pour cause de décès ou transfert en HD) et de décès ont diminuées de façon linéaire au cours de la dernière décennie. La diminution de transfert en HD, observée à partir de 2011, est principalement expliquée par une diminution significative de transfert pour cause infectieuse.

Nos résultats concordent avec les données de la littérature. En effet le risque de péritonite est en constante diminution depuis plusieurs années. Le déploiement de programme d'éducation thérapeutique, l'utilisation de solutions hydroalcoolique ainsi que des changements de pratique internationaux tel que l'antibioprophylaxie à la pose du cathéter

et les soins d'urgence pourraient expliquer ces changements. La diminution du risque de péritonite semble se traduire par une diminution du risque de transfert en HD pour raison infectieuse.

Impact du temps passé en hémodialyse avant un transfert en dialyse péritonéale sur le devenir en dialyse péritonéale

1. Introduction

Malgré la diminution du taux de transfert en HD, cet évènement reste une des causes majeures d'arrêt de la DP. Durant leur parcours, jusqu'à un tiers des patients vont subir un transfert de modalité de dialyse. On considère désormais le parcours des patients comme un parcours de soin intégré qui comprend une succession de différents traitements, les périodes de transition étant des périodes à risque. Le transfert de la DP vers l'HD est l'un des transferts les plus fréquents et a été largement étudié.

Une proportion beaucoup plus faible de patients connaîtra au cours de son parcours un transfert de l'HD vers la DP, en raison d'une préférence du patient ou d'un manque d'abord vasculaire. La survie en DP des patients transférés depuis l'HD en comparaison aux patients ayant d'emblée débuté la DP est controversée. On peut supposer que le temps passé en HD avant un transfert en DP impacte la survie en DP, cependant ceci n'a jamais été décrit dans la littérature.

L'objectif de cette étude était d'étudier l'effet de la transition de l'HD sur la survie technique de la DP (décès ou re-transfert en HD), le décès et le re-transfert en HD ; en prenant en compte l'impact du temps passé en HD avant le transfert en DP.

2. Matériels et méthodes

Cette dernière étude s'est basée sur les données du registre REIN; portant sur 1985 patients ayant débuté l'HD entre le 1^e janvier 2008 et le 31 décembre 2016 et qui ont subi un transfert de l'HD vers la DP. Un modèle de Cox a été utilisé afin d'étudier l'association entre le temps passé en HD avant transfert en DP et les évènements d'intérêt suivant : arrêt de la DP pour décès ou re-transfert en HD (critère composite), décès et re-transfert en HD. La transplantation rénale et récupération de fonction rénale étaient considérés comme évènements compétitifs dans le modèle de Fine and Gray.

3. Résultats

Parmi les 1985 transferts d'HD vers la DP, 1344 (68%) ont eu lieu dans les trois premiers mois en HD, avec une durée médiane en HD de 1.94 mois (interquartile (IQR) 1.02-4.01) avant le transfert en DP. Pour le critère composite de décès ou re-transfert en HD, la survie médiane en DP après cette transition était de 20 mois (IQR 18-21). Le temps passé en HD avant un transfert en DP était associé avec une augmentation du risque d'arrêt de la DP pour décès ou re-transfert en HD (cs-HR 1.01, IC 95% 1-1.02) et du risque de décès (cs-HR 1.02, IC 95% 1.01-1.03), mais n'était pas associé au risque de re-transfert en HD censuré pour le décès. Des résultats similaires ont été observés malgré la prise en compte des évènements compétitifs par un modèle de Fine and Gray.

4. Discussion

Nous avons montré que le temps passé en HD avant un transfert en DP est associé à la survie patient mais pas au risque de re-transfert en HD. L'impact du temps passé en HD sur la survie en DP semble augmenter de façon linéaire avec l'augmentation du temps passé en HD.

Dans le peu d'études s'intéressant à cette transition, le temps passé en HD avant le transfert en DP est dichotomisé en transfert précoce (dans les 3 premiers mois après le début de l'HD) et transfert tardif (au-delà des 3 premiers mois après le début de l'HD). Les raisons du transfert semblent être drastiquement différentes en fonction du délai : les transferts précoces étant principalement en lien avec les préférences des patients dans un contexte de début de la dialyse en urgence, alors que les transferts tardifs sont majoritairement secondaires à un épuisement des voies d'abord vasculaires ou d'une instabilité hémodynamique lors des séances de dialyse. Dans notre étude, une modélisation linéaire du temps passé en HD avant transfert semblait décrire au mieux l'association entre la survie en DP et le temps passé en HD. On peut présumer que l'impact du temps passé en HD avant transfert sur le risque d'arrêt de la DP est présent dès l'initiation de l'HD puis augmente progressivement avec le temps. Si un transfert en DP est envisagé, il devrait être préparé et organisé le plus rapidement possible afin de limiter la durée passée en HD.

Discussion

1. Résultats principaux

Les résultats de nos travaux de recherche sont complémentaires aux recherches en cours visant à mieux comprendre l'utilisation de la DP, dans le but d'intensifier les efforts pour augmenter d'avantage l'accès à la DP pour les patients insuffisants rénaux chroniques en Europe. Nos résultats sont notamment intéressants pour les patients âgés et fragiles, une population souvent privée de la possibilité de dialyse à domicile.

Premièrement, nous avons décrit comment l'introduction d'un programme de DP assistée a positivement influencé l'initiation de la DP et a permis de contrebalancer la diminution des taux de DP initialement observés. Par la suite, nous avons rapporté la baisse

constante et linéaire de l'assistance par un membre de la famille, qui a conduit à une diminution de l'utilisation de la DP assistée jusque 2013. L'augmentation secondaire de l'utilisation de la DP assistée, observée à partir de 2013, est principalement le résultat d'une augmentation de l'utilisation d'assistance par infirmière, ce qui pourrait être expliqué par l'introduction d'incitation économique en 2011 permettant le remboursement de l'assistance par infirmière dans les EHPADs. Nos résultats montrent qu'en raison d'une diminution de l'assistance par la famille, la DP assistée repose actuellement sur l'assistance par infirmière. Ensuite, nous avons montré que le risque d'arrêt de la DP (due à un décès ou un re-transfert en HD) et le risque de décès ont diminué de façon linéaire au fil du temps. La diminution des taux de transfert en HD observée depuis 2011 est principalement en lien avec une diminution des transferts pour cause infectieuse. Finalement, nous avons démontré que le transfert de l'HD vers la DP est un évènement rare qui intervient précocement dans la prise en charge de l'IRCT. Le temps passé en HD avant un transfert en DP impacte la survie du patient mais sans effet sur le risque de re-transfert en HD. L'effet du temps passé en HD sur le risque d'arrêt de la DP semble augmenter progressivement au fil du temps.

2. Perspectives

A la lumière des résultats de cette thèse, il persiste des interrogations sur l'utilisation de la DP. Par ailleurs, les patients âgés en insuffisance rénale terminale ont rarement accès à une prise de décision partagée sur leur prise en charge puisque la possibilité d'un traitement à domicile ou d'une transplantation leur est rarement proposée. Plusieurs projets de recherche découlent des résultats de ce travail de thèse, afin de répondre à ces interrogations.

Tout d'abord, nous avons décrit dans notre travail une diminution du risque de transfert en HD pour cause infectieuse, ce qui pourrait s'expliquer par le développement de

programmes d'éducation thérapeutique et des changements internationaux des pratiques médicales. Toutes ces mesures devraient permettre de diminuer les péritonites induites par une contamination par des germes cutanés, principalement des péritonites à cocci gram positif. Très peu d'études rapportent les tendances temporelles des résultats microbiologiques des péritonites. Nous souhaitons étudier les tendances temporelles des germes responsables de péritonites au cours du temps, en France, afin d'évaluer l'impact des mesures préventives sur la contamination par des germes cutanés. En utilisant les données du RDPLF, nous souhaitons explorer l'association entre le temps et les différents germes responsables de péritonites, en utilisant un modèle de Cox à variance robuste. Notre hypothèse principale est que le taux de péritonites à gram-positif a diminué au fil du temps, ce qui soulignerait l'efficacité des programmes d'éducation thérapeutiques et des mesures d'hygiène préventives. Par ailleurs, nous souhaitons évaluer l'évolution du risque de base d'échec de DP et de péritonite en fonction du statut d'assistance (patients autonomes versus patients assistés) en utilisant un modèle de Royston. Cette modélisation se libère de l'hypothèse des risques proportionnels présumée comme vraie dans un modèle de Cox. En effet cette hypothèse est souvent déraisonnable dans les études épidémiologiques, puisque l'effet d'un facteur d'exposition sur un évènement peut changer au cours du temps.

Secondairement, en 2018, l'âge médian des patients à l'initiation du traitement d'EER était de 70,4 ans en France. L'âge en soit ne constitue pas une contre-indication formelle à la transplantation rénale. Cependant en France en 2012, l'âge médian des patients transplantés rénaux était de 49 ans, avec seulement 9,7% des transplantations rénales effectuées chez des patients âgés de plus de 70 ans. En Europe, l'accès à la transplantation rénale pour les personnes âgées prévalentes en IRCT a augmenté de 0.3% en 2005 à 0.9% en 2014, avec une variation importante entre les pays. La majorité des greffons alloués à ces patients provient

de donneurs décédés âgés. L'utilisation de donneurs décédés à critères élargis pourrait donc en partie expliquer cette augmentation. Plusieurs études décrivent une amélioration de la survie chez les patients âgés recevant une transplantation rénale, avec également une amélioration de la survie de ces greffons, au cours des dernières décennies. Malgré ces résultats encourageants, l'accès à la transplantation rénale pour cette population reste limité en Europe et en France. Dans les recommandations HAS de 2015 « Transplantation rénale - accès à la liste d'attente nationale », il est recommandé d'effectuer un bilan pré-transplantation rénale jusqu'à 85 ans, en l'absence d'autre contre-indication à la transplantation. Cette recommandation, en élargissant le critère d'âge, contraste avec les pratiques antérieures qui limitaient l'accès à la greffe pour les sujets âgés. Nous souhaitons réaliser une étude portant sur l'évolution du taux d'inscription sur la liste de transplantation rénale des patients âgés de plus de 70 ans incidents en EER au cours de la dernière décennie, et de l'impact des recommandations HAS afin de promouvoir la greffe chez le sujet âgé publiées en octobre 2015. Cette étude rétrospective nationale porterait sur les patients âgés de 70 ans et plus, incidents en EER entre le 01/01/2010 et le 31/12/2019, inscrits dans REIN. L'objectif de ce travail serait de décrire l'évolution au cours du temps sur la période d'étude, du taux d'inscription sur la liste de transplantation rénale, et d'estimer l'impact de la publication des recommandations HAS 2015 sur cette évolution. Nous souhaiterions réaliser une modélisation de Poisson, avec comme évènement d'intérêt principal l'inscription sur la liste de transplantation rénale. Ce modèle permettra de présenter la vitesse instantanée d'occurrence de l'évènement, l'effet dépendant du temps et de prendre en compte l'exposition aux recommandations HAS de 2015 en variable dépendante du temps.

Finalement, il existe une grande variation d'utilisation de la dialyse à domicile (DAD) en fonction des différents pays à travers le monde. En Nouvelle-Zélande, jusqu'à 50% des

patients sont dialysés à domicile. Cette proportion chute à 30% en Australie, 20% au Canada, 19% au Royaume-Uni et 7% en France. Plusieurs facteurs peuvent expliquer ces variations d'utilisation de la DAD, notamment au niveau national les différentes stratégies de santé publique (PD first policy) et de remboursement de soins. Une partie de cette disparité peut également s'expliquer par les caractéristiques des centres de dialyse et des caractéristiques patients. La majorité des études disponibles dans la littérature sont basées sur des registres nationaux, prodiguant des renseignements sur la place de la DAD au niveau national mais ne permettant pas de décrire les variations d'utilisation entre les différents pays. En combinant les données de plusieurs registres nationaux dans une même étude, nous pourrions explorer et donc mieux comprendre les variations d'utilisation de la DAD entre différents pays. Au vu des grandes disparités d'utilisation de la DAD à travers le monde, nous souhaitons mener un projet de recherche international portant sur la place de la DAD (DP et HDD) dans les pays suivants : la France, le Royaume-Uni, le Canada, l'Australie, la Nouvelle-Zélande et les Etats-Unis. Nous travaillerions en collaboration, avec les données des différents registres nationaux (Registre REIN, UK Renal Registry-UKRR, Canadian Organ Replacement Registry-CORR, Australia and New-Zealand Dialysis and Transplant registry-ANZDATA et US Renal Data System-USRDS). Les analyses seraient réalisées de manière identique sur chaque registre séparément (sans croisement ni extractions de données entre les différents pays), afin de décrire l'utilisation de la dialyse à domicile dans chaque pays participant à l'étude ainsi que les variations d'utilisation entre les pays. Cette étude aurait pour objectif principal d'étudier dans chaque pays participant à l'étude l'incidence de la dialyse à domicile (DP et HDD), ainsi que les caractéristiques des patients en dialyse à domicile et les différentes approches nationales de déploiement de ces modalités de dialyse (système de santé publique et de remboursement). Afin de décrire l'incidence annuelle ajustée, nous souhaiterions réaliser une

incidence annuelle cumulée ainsi qu'une modélisation de Poisson, avec comme évènement d'intérêt principal l'initiation d'une modalité de DAD (DP et/ou HDD) dans la première année suivant le début de l'EER. En utilisant les données de plusieurs registres nationaux, nous espérons pouvoir fournir une meilleure estimation des variations d'utilisation de la DAD dans différents pays.

3. Conclusion

Dans l'intérêt d'une décision médicale partagée, les patients devraient pouvoir recevoir une éducation thérapeutique et un libre choix quant à leur modalité de suppléance rénale, ce qui implique que toutes les modalités soient disponibles. Il est donc nécessaire que les centres de dialyse soient en mesure de proposer non seulement de la DP, mais également les différentes modalités de DP et donc de la DP assistée. Une large promotion de la DP assistée pourrait permettre à un plus grand nombre de patients de choisir l'option qui correspond le mieux à ses préférences et attentes, en particulier pour les sujets âgés et fragiles. Plusieurs raisons pourraient expliquer pourquoi l'utilisation de la DP reste faible en Europe, avec une connexion entre ces différents obstacles. On pourrait raisonnablement penser qu'une seule intervention ne suffira pas à inverser cette tendance. Cependant, à la lumière des résultats de ce travail, nous pensons que des incitations économiques favorisant le remboursement de la DP assistée ajoutées à un changement de mentalité et un intérêt accru pour la DP pourraient permettre d'augmenter avec succès l'utilisation de la DP et permettre aux patients d'avoir un libre choix quant à leur traitement de suppléance.

La dialyse à domicile dans le traitement de l'insuffisance rénale chronique terminale

Résumé : L'utilisation de la dialyse péritonéale (DP) a diminué au cours des dernières décennies en Europe, en raison notamment d'un faible taux d'initiation et de la persistance d'un taux élevé d'arrêt de cette modalité de dialyse. Des stratégies visant à augmenter l'utilisation de la dialyse à domicile, tel que des programmes de DP assistée, ont été mis en place, cependant leur impact reste inconnu. Dans le cadre de ce travail, des modèles de Cox à variance robuste avec si besoin des modélisations par polynômes fractionnels et variables dépendantes du temps, ont été réalisés afin de décrire l'évolution au cours des dernières décennies de l'utilisation et de la survie en DP. Nous avons décrit comment l'introduction d'un programme de DP assistée a positivement influencé l'initiation de la DP et a permis de contrebalancer la diminution des taux de DP initialement observés. En France, la DP assistée repose sur l'assistance par infirmière, qui peut être développée avec succès via des incitations économiques. Le risque d'arrêt de la DP (due à un décès ou un re-transfert en HD) et le risque de décès ont diminué de façon linéaire au fil du temps, la diminution des taux de transfert en HD étant principalement en lien avec une diminution des transferts pour cause infectieuse. Finalement, nous avons démontré que le temps passé en HD avant un transfert en DP impacte la survie du patient mais sans effet sur le risque de re-transfert en HD. Nous pensons que des incitations économiques favorisant le remboursement de la DP assistée ajoutées à un intérêt accru pour la DP pourraient permettre d'augmenter avec succès l'utilisation de la DP et permettre aux patients d'avoir un libre choix quant à leur traitement de suppléance.

Mots clés : dialyse à domicile, dialyse péritonéale, assistance, études temporelles, insuffisance rénale chronique

Home dialysis for the treatment of end stage chronic kidney disease

Abstract: Peritoneal dialysis (PD) utilization has been declining over the past decades in Europe. Several reasons could explain this PD under-utilization, such as a low PD uptake and the persistence of an elevated rate of PD cessation. Strategic incentives to increase home dialysis, such as assisted PD programs, have been developed, however their impact remains under-described. In this work, we combined data of patients on PD from France and the UK, using statistical models including time-varying covariate, fractional polynomials and Cox regression with robust variance, to address some of the gaps in the current knowledge in PD under-utilization. With the present thesis, we have reported how the introduction of an assisted PD service positively influenced the uptake of PD and counterbalanced the decline in PD rates over time. In France, assisted PD currently relies on nurse assistance; which can be successfully promoted with economic incentives. Both PD cessation (due to either death or transfer to HD) and death linearly declined over time, and transfer to HD declined from 2011 mainly because of a significant decline in infection-related transfers. Finally, we have shown that time spent on HD before transfer to PD impacts patient survival but does not impact retransfer to HD. In lights of the results of this work, we believe that economic incentives promoting the reimbursement of assisted PD added with a shift in mentality and an increased commitment to PD could successfully increase PD rates and enable patients to have a free choice regarding their treatment modality.

Key words: home dialysis, peritoneal dialysis, longitudinal trends, assisted peritoneal dialysis, chronic kidney disease