A COMPARISON OF TECHNIQUE SURVIVAL IN CANADIAN PERITONEAL DIALYSIS AND HOME HEMODIALYSIS PATIENTS

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Contribution of Authors

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Dr. James Hanley contributed to design, analysis, interpretation of data and revision of Chapters 1 and 2.

Dr. Annie-Claire Nadeau-Fredette contributed to data interpretation and revision of the manuscript (Chapter 2).

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List of Abbreviations

AHR	adjusted hazard ratio
APD	automated peritoneal dialysis
AVF	arteriovenous fistula
AVG	arteriovenous graft
BMI	body mass index
CAPD	continuous ambulatory peritoneal dialysis
CORR	Canadian Organ Replacement Register
CVC	central venous catheter
ESKD	end-stage kidney disease
HD	hemodialysis
HHD	home hemodialysis
HR	hazard ratio
PD	peritoneal dialysis
PS	propensity score
RRT	renal replacement therapy

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Abstract

Background: High discontinuation rates remain a challenge for home hemodialysis (HHD) and peritoneal dialysis (PD). We compared technique failure risks among Canadian patients receiving HHD and PD.

Methods: Using the Canadian Organ Replacement Register, we studied adult patients who initiated HHD or PD within 1 year of beginning dialysis between 2000-2012, with follow-up until December 31 2013. Technique failure was defined as a transfer to any alternative modality for a period of ≥60 days. We compared technique survival between HHD and PD using a Fine and Gray competing risk model. Secondary outcomes included the time dependence of technique survival, the association of patient characteristics with technique failure, causes of technique failure and changes in technique failure rates over time

Results: Between 2000-2012, 15,314 patients were treated with a home dialysis modality within 1 year of dialysis initiation: 14,461 on PD and 853 on HHD. Crude technique failure rates were highest during the first year of therapy for both home modalities. During the entire period of follow-up, technique failure was lower with HHD compared to PD (adjusted hazard ratio [AHR] 0.79; 95% CI 0.69-0.90). However, the relative technique failure risk was not proportional over time and the beneficial effect of HHD was only apparent after the first year of dialysis. Comparisons also varied among subgroups and the superior technique survival associated with HHD relative to PD was less pronounced in more recent years and among older patients. Predictors of technique failure also differed between modalities. While obesity, smoking and small facility size were associated with higher technique failure in both PD and HHD, the effect of age and gender differed. Furthermore, the majority of home dialysis discontinuation occurred for medical

reasons in PD (38%) while the majority of HHD patients experienced technique failure due to social reasons or inadequate resources (50%).

Conclusions: In this Canadian study of home dialysis patients, HHD was associated with better technique survival compared to PD. However, patterns of technique failure differed significantly among these modalities. Strategies to improve patient retention across all home dialysis modalities are needed.

Abrégé

Introduction: Les taux d'abandon élevés restent un défi pour l'hémodialyse à domicile et la dialyse péritonéale. Le but de notre étude était de comparer les risques d'échec technique entre l'hémodialyse à domicile et la dialyse péritonéale au Canada.

Méthodes: À l'aide du Registre CORR (Canadian Organ Replacement Register), nous avons étudié les patients adultes ayant initié l'hémodialyse à domicile ou la dialyse péritonéale au cours de l'année suivant le début de la dialyse entre 2000 et 2012. Nous avons défini l'échec technique comme un transfert vers une modalité de dialyse alternative pour une période de ≥60 jours. Nous avons comparé la survie technique entre l'hémodialyse à domicile et la dialyse péritonéale en utilisant un modèle de risque concurrent Fine and Gray. Nous avons aussi examiné la dépendance temporelle de la survie technique, l'association des caractéristiques du patient avec l'échec technique, les différentes causes d'échec technique et la variation des taux d'échec technique au fil du temps.

Résultats: Entre 2000 et 2012, 15 314 patients ont été traités avec une modalité de dialyse à domicile dans l'année suivant le début de la dialyse: 14 461 sous dialyse péritonéale et 853 sous hémodialyse à domicile. Les taux d'échec technique étaient les plus élevés au cours de la première année de traitement pour les deux modalités à domicile. Pendant toute la période de suivi, l'échec technique était plus faible avec l'hémodialyse à domicile que dialyse péritonéale (risque ajusté [AHR] 0,79; 95% CI 0,69-0,90). Cependant, le risque relatif d'échec technique n'était pas proportionnel au fil du temps et l'effet bénéfique de l'hémodialyse à domicile n'était apparent qu'après la première année de dialyse. Les comparaisons variaient également entre les sous-groupes et la survie technique supérieure associée à l'hémodialyse à domicile par rapport à la dialyse péritonéale était moins prononcée au cours des dernières années et chez les patients plus

âgés. Les facteurs prédictifs d'échec technique différaient également d'une modalité à l'autre. Alors que l'obésité, le tabagisme et les centres traitants plus petits étaient associés à un échec technique plus élevé, à la fois pour l'hémodialyse à domicile et la dialyse péritonéale, les effets de l'âge et du sexe était différents. En outre, la majorité des discontinuations de dialyse à domicile ont eu lieu pour des raisons médicales pour la dialyse péritonéale (38%), tandis que la majorité des patients sous hémodialyse à domicile ont connu un échec technique pour des raisons sociales ou des ressources insuffisantes (50%).

Conclusions: Au Canada, l'hémodialyse à domicile était associée à une meilleure survie technique par rapport à la dialyse péritonéale. Cependant, les variations d'échec technique différaient de manière significative entre ces modalités. Des stratégies visant à améliorer la survie technique chez les patients sous toutes modalités de dialyse à domicile sont nécessaires.

Introduction

End-stage kidney disease is associated with increased mortality, morbidity and impaired quality of life. Peritoneal dialysis (PD) and home hemodialysis (HHD) are renal replacement modalities that allow patients to manage their own treatment in the comfort of their own home and offer several clinical benefits. With worldwide growing interest in increasing utilization of home dialysis, less is known on how to prevent discontinuation of these modalities. Indeed, high rates of discontinuation ("technique failure") remain a challenge. While previous studies have examined some of the predictors of technique failure for PD and HHD, few studies have compared technique survival between these home modalities.

Our first objective was to review the literature on what is currently known about all aspects of technique survival for both PD and HHD, including what definitions are used, what are the reported rates of technique failure, what are the clinical and sociodemographic predictors of technique failure and what are the most common causes of discontinuation.

Our second objective was to compare the patterns and trajectory of technique survival between these home modalities in a multicenter Canadian cohort to have a better understanding on technique survival.

Chapter 1:

Technique Survival in Home Dialysis: A Narrative Review

Home dialysis therapies, including home hemodialysis (HHD) and peritoneal dialysis (PD), offer several benefits for patients with end-stage kidney disease when compared with patients on conventional in-center thrice-weekly hemodialysis (HD). HHD is associated with improvements in blood pressure control, abnormalities of mineral metabolism, sleep quality, and regression of left ventricular hypertrophy[1-6]. In contrast, peritoneal dialysis (PD) is associated with better preservation of residual kidney function, avoidance of vascular access complications, and lower infection rates. [7] In addition to numerous clinical benefits, many studies have also shown that home dialysis modalities are associated with improved quality of life [2,8-10] and significantly lower costs[11] when compared to in-center HD. Moreover, these modalities allow patients the autonomy of directing their own treatment as well as the flexibility to adjust their dialysis treatment schedule while avoiding the time and cost of frequent travel to a dialysis center. Despite these advantages, in-center conventional HD remains the most common form of renal replacement therapy in at least 80% of ESRD patients in the majority of the world.[12] However, interest in home dialysis has grown significantly in recent years. In Canada, home dialysis is achieved in 25-30% of patients[12] with ongoing efforts to increase the incidence of home dialysis therapies. However, high rates of discontinuation, defined as "technique failure", remain a challenge. In fact, rates have been reported in up to 25% of patients within the first year of therapy for both HHD and PD.[13-17] Little is known on what patient or center-specific characteristics predict technique failure and what factors are potentially modifiable.

Challenges in defining technique failure

Technique failure is defined as a transfer to an alternative dialysis modality for a predetermined amount of time. It remains unknown what optimal time period most accurately defines technique failure or is associated with adverse outcomes. Studies have used a variety of definition including 30, 45, 60, 90, and 180-days. As changes may often be temporary in the context of an acute illness or a hospitalization, too short a time frame used for the definition of technique failure may not accurately represent true discontinuation as patients may return to their initial modality. Conversely, using a longer time frame may give rise to patients getting loss to follow-up or developing other complications unrelated to technique failure. Moreover, another challenge is that some modality changes may be due to inadequate resources (i.e. a patient relocates to a jurisdiction where home dialysis is not supported) and may not truly represent technique failure.

Given the lack of a standardized definition of technique failure, it is difficult to accurately determine clinical implications on outcomes and compare studies. In a recent study of PD patients by Lan et al. using the Australia and New Zealand Dialysis and Transplant Registry, the likelihood to return to PD was highest when using a 30-day definition but was very small with definitions >180 days.[18] A 30-day definition allowed to capture acute intercurrent illness contributing to increased morbidity and mortality while a 180-day definition provided a time-frame where it was unlikely the patient would return to PD. As such, the authors emphasized that different definitions addressed distinct clinical aspects.

Complications associated with Technique Failure

Technique failure usually leads to transition to conventional in-center HD.[19,20] For PD patients, this transition is often in context of an acute medical complication, most commonly PD peritonitis,

failure of PD to provide adequate dialysis or PD catheter malfunction.[20] Therefore, this switch is may be unplanned.[19] With an unplanned transition, patients likely initiate HD with a central venous catheter and it is well recognized that there is a higher mortality associated with unplanned HD initiation, especially with catheter use and its associated higher infectious risks.[21,22] Moreover, this transition period may also be associated with psychosocial distress and changes in quality of life. For HHD, modality change is also associated with poor outcomes. In a study by Shah et al., the 90-day mortality in patients who experienced HHD technique failure was significantly higher (26%) compared to patients who remained on HHD.[23] Nevertheless, the transition period from one renal replacement therapy to another is a particularly vulnerable time, both in context of the acute medical issues leading to technique failure, but also due to the unplanned nature of the transition. Therefore, it is imperative to find strategies not only to prevent technique failure, but also to ensure a better and smoother transition between renal replacement modality.

Technique Survival in Peritoneal Dialysis

Rates of technique failure

Rates of technique failure vary considerably in the literature.[15-17,20,24-26] Discontinuation appear to be highest during the first year of therapy, with rates varying from 4.9% to 26.2%.[16,17,24,25] Median time to technique failure has been reported at about 2 years.[17,27]

Predictors of technique failure

Various patient and center-specific factors appear to be associated with technique failure. A higher degree of comorbidity appears to lead to increased risk, with BMI, diabetes, smoking,

cardiovascular disease, peripheral vascular disease and chronic lung disease having all been shown to predict technique failure.[15,24,26] In contrast, the effect of age on technique failure is variably reported. In some studies, older patients have been shown to have increased technique failure risk[16,24,26] whereas other studies have shown a lower risk in patients >65 years old.[28] This may be related to increasing utilization of assisted PD in older patients in some areas of the world which may be associated with better technique survival.[29]

Sociodemographic factors have also been shown to be strong predictors of technique survival. In fact, studies have demonstrated racial disparities both in the use of and in outcomes with home dialysis.[30] In a recent study by Mehrotra et al in the US, Black patients treated with PD had a much higher risk of technique failure compared to Caucasians.[30] Furthermore, employment status has also been identified as a determinant of technique survival with full-time employment having been demonstrated to be a strong and independent predictor of better technique survival.[31,32] In a Chinese study, lower income was also found to predict treatment failure.[33]

Other factors that have been demonstrated to impact technique survival have included timing of referral to a nephrologist and center-specific factors. Late referral to a nephrologist has consistently been shown to be associated with higher technique failure risk.[16,17,26] Furthermore, center experience with PD appears to be an important determinant of technique success. Indeed, many studies including a systematic review have demonstrated that larger centers and centers with a higher proportions of PD patients have lower rates of technique failure.[26,34-36] These findings likely reflect the degree of experience managing PD patients and their associated complications in addition to availability of resources.

Causes of technique failure

Although exact causes for PD discontinuation are not always discernable in retrospective studies, the most common reported reasons for technique failure have been mechanical causes (leaks, catheter dysfunction, hernias, etc.), infection, inadequate dialysis and psychosocial issues.[20,24]

Technique Survival in Home Hemodialysis

Rates of technique failure

The complex and frequent nature of HHD may lead to patient and/or caregiver burnout, thus leading to discontinuation with transfer to in-center conventional HD. Reported rates of technique failure vary considerably in the literature with 1-year rates between 2 and 25%.[13,37] In a Canadian multicenter study from 1994-2006, technique survival was 98% and 95% at 1 and 5 years, respectively.[38] Conversely, in an Australian cohort, technique survival rates were reported at 90% and 68% at 1 and 5 years.[39] More recently, a US study described much higher discontinuation rates of 25% at 1 year and 35% at 2 years.[40] These significant differences in rates of technique failure are likely related to center-specific practice patterns, evolving patient characteristics and likely less strict selection criteria in recent years with patients with a higher degree of comorbidity being treated with HHD.

Predictors of technique failure

Compared to PD, less is known about factors associated with technique failure in HHD. Clinical characteristics predicting technique failure have included age, diabetes, and heart failure.[37,38,40]

Socioeconomic factors also appear to contribute importantly to technique failure risk. In fact, substance use and urban residence have both been shown to predict HHD discontinuation. [37,40] More recently, a US cohort study by Mehrotra et al. demonstrated that Black patients were more likely to experience technique failure, even after adjustment for clinical factors, thus further supporting an important role for socioeconomic status.[30] Center characteristics have also been shown to be important predictors of technique failure. In a multicenter Canadian cohort study of 7 treating centers, Pauly et al demonstrated that there were significant variations in rates of technique failure among the treating centers that were not attributable to differences in patient characteristics.[41]

Causes of technique failure

As compared to PD, less is known about exact causes of discontinuation of HHD. In a recent study of 94 Canadian HHD patients, the reported causes for modality change were medical instability (65%), patient burnout (13%), caregiver burnout (13%) and patient choice (9%).[23]

Conclusion

With increasing efforts to encourage home modalities, it is imperative to better understand technique survival and find strategies to help maintain patients on the home therapy of their choosing. Can hsigh-risk patients be identified early and managed appropriately? Can there be improvements with patient training? What center-specific practices are potentially modifiable to improve technique survival? Moreover, it is also important to note that by expanding patient selection criteria to increase utilization of home dialysis, this may also lead to higher discontinuation rates.

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Preamble to Chapter 2

With increasing evidence of clinical benefits with home dialysis, efforts are being made to increase uptake of home dialysis modalities. Many centers are even promoting a "home first" approach. However, in addition to encouraging increasing utilization of home dialysis modalities, it is also imperative to elucidate the best strategies in order to maintain patients on these therapies. As such, a better understanding of predictors, patterns and preventative measures for technique failure is crucial. Moreover, in order to provide insight on trajectories and patterns of technique failure, it would be useful to compare and contrast technique survival between these two home dialysis modalities. With this knowledge, this would allow us to better educate our patients on home dialysis therapies and expand on what to expect with each modality in order to make a more informed decision.

As such, our next Chapter will aim to provide insight on home dialysis technique survival by exploring the differences in patterns and trajectory of technique survival between peritoneal dialysis and home hemodialysis.

Chapter 2:

A Comparison of Technique Survival in Canadian Peritoneal Dialysis and Home Hemodialysis Patients

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Introduction

Interest in home dialysis has grown in recent years. Indeed, home hemodialysis (HHD) and peritoneal dialysis (PD) offer several clinical benefits for patients with end-stage kidney disease (ESKD) when compared with conventional facility-based thrice-weekly HD. While there has been increasing utilization of home dialysis in many areas of the world[1], high rates of technique failure remain a challenge. In fact, rates have been reported in up to 25% of patients within the first year of therapy for both HHD and PD.[2-6] While previous studies have examined some of the determinants of technique survival for HHD and PD, few studies have compared the trajectory of technique survival between these home modalities.

The primary aim of this study was to better understand home dialysis technique failure by directly comparing time-specific patterns of technique failure between PD and HHD. Our secondary aims were to examine the time dependence of technique survival, the association of patients characteristics with technique failure, causes of technique failure, and changes in technique failure rates over time.

Methods

This registry-based cohort study included adult patients (aged ≥ 18 years at time of dialysis initiation) who initiated either PD or HHD in Canada within 1 year of renal replacement therapy (RRT) initiation between January 1, 2000 and December 31, 2012. The end of the observation period was December 31, 2013. For the direct comparison of technique survival between PD and HHD, patients who were treated with both modalities within the first year of dialysis initiation were excluded. Patients were identified from the Canadian Organ Replacement Register (CORR),

a validated national registry that captures the incidence, prevalence and outcomes of >99% chronic dialysis patients and solid-organ transplant recipients in Canada.[7] Data was collected by completion of a registration form for each patient by the dialysis provider at initiation of dialysis and yearly thereafter. Data from the province of Quebec was excluded due to the need for additional ethics and data permissions. Approval for the study was received from the research ethics board at the University Health Network in Toronto, Canada and from CORR.

Exposure and covariates

PD was defined as treatment with either continuous ambulatory PD (CAPD) or automated PD (APD), also including home-assisted PD. HHD was defined as any hemodialysis performed at home (conventional, short-daily or nocturnal). Baseline comorbidities were documented by the individual facilities using the CORR registration form at time of dialysis initiation. CORR data has been recently validated.[8] For patients treated with HHD, vascular access type was ascertained at time of first HHD treatment. Late referral was defined as never having been seen by a nephrologist before dialysis initiation or first seeing a nephrologist within 3 months before starting dialysis. For each individual center, the average number of new patients per year was calculated. Center size was then categorized as small or large based on a cut-off, defined as the median number of new patients per year for PD and HHD, respectively.

Outcomes

The primary outcome of interest was technique failure. Technique failure was defined as a transfer to any alternative dialysis modality for a period of ≥60 days. Intervals shorter than 60 days were

not considered as they were deemed likely to be interruptions due to hospitalization or an acute medical illness.

Secondary outcomes included (1) comparison of technique failure between PD and HHD among different prespecified patient subgroups, (2) association of patient characteristics with technique failure for each home modality, (3) temporal changes in technique failure rates over time, and (4) return rates to initial modality using different technique failure time cut-offs.

Statistical Analyses

Baseline characteristics of the cohort are presented as medians with interquartile range for continuous variables and proportions for categorical variables. For the direct comparison of technique failure between HHD and PD, we used a competing risk regression model based on the proportional hazards model for the subdistribution of Fine and Gray.[9] A Fine and Gray model allowed us to take into account the effect of informative censoring caused by potential differences in rates of mortality and kidney transplantation between PD and HHD, events which were both treated as competing risks. We calculated overall HRs, but, as the association was not proportional over time, year-specific HRs from the time of dialysis initiation were also calculated. To assess the predictors of technique failure for each home dialysis modality independently, a competing risk regression model was also used. Censoring events included loss to follow-up or being alive at the end of the observation period (December 31, 2013), whereas mortality and transplantation were treated as competing risks. A comparison of technique survival between HHD and PD was also performed within various pre-specified subgroups (age, year of dialysis initiation, initial HHD vascular access, HHD treatment type)

Results were validated with a propensity-score (PS) model. The PS was obtained from a logistic regression model using the following covariates at start of follow-up: age, gender, race, BMI, cause of ESKD, era of treatment, diabetes, coronary artery disease, cerebrovascular disease, peripheral vascular disease and smoking status. A 1:1 PS nearest neighbour matching was performed without replacement and technique survival was compared between the matched dialysis modality groups using a Fine and Gray competing risk model. Standardized differences before and after matching were calculated (Figure S1).

Sensitivity Analyses

To test the robustness of our findings, a sensitivity analysis was performed to assess the primary outcome based on a definition of technique failure of the requirement of at least 90 days on a different dialysis modality (compared to 60 days in the primary analysis).

Results

Baseline characteristics

Between January 1, 2000 and December 31, 2012, a total of 15,314 patients were treated with a home dialysis modality within 1 year of RRT initiation in the CORR: 14,461 patients on PD and 853 patients on HHD. Median follow-up was 33.4 months for PD patients and 30.8 months for HHD patients. Table 1 details the baseline characteristics of the entire study cohort, separately for each home dialysis modality. 51 patients were treated with both PD and HHD within the first year and therefore were excluded in the analysis directly comparing technique failure between both modalities. Patients receiving PD were older (46% of patients ≥65 years in PD vs 23% in HHD) and were also more likely to have diabetic kidney disease while HHD patients were more likely to

have glomerulonephritis and polycystic kidney disease as a cause of ESKD. Furthermore, HHD patients had fewer comorbidities with a lower prevalence of coronary artery disease, cerebrovascular disease and peripheral vascular disease. The median center size for PD was 30 new patients per year (IQR 19-45) and the median center size for HHD was 5 new patients per year (IQR 3-7). Thus, these values were used as cut-off to categorized small vs. large centers.

Comparison of technique survival between PD and HHD

There were 5874 technique failure events in PD patients (16.9 per 100 person-years) and 281 events in HHD patients (13.3 per 100 person-years). The median technique survival was 47.9 months for PD and 75.6 months for HHD. Variations in technique failure rates were significantly different between both modalities (Figure 1). Crude rates were the highest during the first year of therapy for both modalities (19.4 per 100 person-years in PD and 22.0 per 100 person-years in HHD). Among HHD patients, rates were significantly lower subsequent to that. In contrast, the decrease in rates was not as pronounced among PD patients

Kaplan-Meier curves comparing unadjusted technique survival in HHD and PD are presented in Figure 2 (log rank $p<0.01$). 1-, 2-, and 5-year technique survival were 83% , 71% and 43% in PD vs. 82%, 76%, and 59% in HHD. In a multivariate competing risk model, the overall adjusted risk of technique failure was significantly lower with HHD compared to PD (adjusted HR [adjusted hazard ratio] 0.79; 95% CI 0.69-0.90, Table 2). However, technique failure comparisons were not proportional over time. For the first year of dialysis, there was no significant difference in technique failure between HHD and PD (AHR 1.13; 95% CI 0.94-1.36). Subsequent to the first year, the risk of technique failure was significantly lower with HHD (Year 2: AHR 0.46 95% CI

0.33-0.65; Year 3: AHR 0.51, 95% CI 0.35-0.75; Year 4: AHR 0.30, 95% CI 0.16-0.55; >4 years: AHR 0.65, 95% CI 0.45-0.94, Table 2). In the propensity-matched cohort, results were similar to the primary analysis.

Subgroup analysis

The relative risk of technique failure of HHD compared to PD varied among different subgroups (Figure 3, Table S1). Indeed, HHD was associated with lower technique failure in the subgroup of patients aged <50 years (AHR 0.60; 95% CI 0.46-0.78) and 50-65 years (AHR 0.75; 95% CI 0.61-0.93) compared to PD, but there was no significant difference among patients ≥ 65 years old (AHR 1.24; 95% CI 0.98-1.58). Furthermore, while the adjusted risk of therapy discontinuation was lower among the HHD group for patients initiating dialysis from 2000-2008, this difference was not seen among patients initiating home dialysis in the most recent era of 2009-2012 (AHR 1.01; 95% CI 0.83-1.23). The relative superior technique survival of HHD compared to PD was also more pronounced in patients who initiated HHD with an arteriovenous access and in those who were treated with slow-nocturnal or short-daily HHD.

Association of patient characteristics with technique failure

The patient characteristics associated with technique failure are presented in Table 3. While some factors predictive of technique failure were similar among PD and HHD patients, there were some important differences. Black race, BMI ≥30 kg/m^2, smoking, and small facility size were associated with an increased risk of technique failure in both PD and HHD. However, the effect of age on technique survival differed between both modalities. Age ≥65 years was associated with an increased risk in HHD patients whereas there was no significant effect of age in PD patients. There

was equally a higher technique failure risk in male PD patients while there was no significant gender association among HHD patients. Among PD patients, a primary renal disease of glomerulonephritis and renovascular disease was associated with a lower technique failure risk compared to diabetic kidney disease. Comparatively, only polycystic kidney disease and "other" category as a cause of ESKD were predictive of therapy discontinuation among HHD patients. Lastly, the effect of the era of treatment varied between these two home dialysis modalities. Initiation of therapy in the 2009-2012 era was associated with a lower adjusted risk of technique failure among PD patients, while it was associated with a higher adjusted risk for HHD patients compared to the 2000-2004 cohorts.

Temporal trends in technique failure

Crude technique failure rates by year of dialysis initiation for PD and HHD are presented in Figure 4. PD technique failure rates appeared to be overall stable over time, while there appears to be an increase in failure rates among HHD since 2002.

Causes of technique failure

Causes of technique failure were significantly different between PD and HHD (Table 4). While the majority of technique failure occurred for medical reasons in PD (peritonitis, other abdominal complications, inadequate dialysis), the majority of HHD patients experienced technique failure due to social reasons or inadequate resources.

Different technique failure cut-off definitions

Technique failure events and rates using different definitions (30 days, 60 days, 90 days, 180 days and 365 days) are presented in Table 5. The proportion of patients returning to their initial home modality after 30-days of technique failure was 9.4% for PD and 16% for HHD within one year. After 60 days, this decreased to 6.5% for PD and 8.5% for HHD. After 90 days, only 4.1% of PD patients and 5.8% of HHD patients returned to their initial home modality within one year.

Sensitivity Analyses

Using a technique failure definition of 90 days, the comparisons between PD and HHD yielded very similar adjusted HRs to our primary analysis (Table S2).

Discussion

In this Canadian study of home dialysis patients, HHD was associated with overall superior technique survival compared to PD. However, patterns of technique survival differed significantly among these modalities. When directly comparing technique survival, the beneficial effect of HHD was only apparent after the first year of dialysis. Moreover, comparisons also varied among subgroups, especially among different age groups and treatment era. Causes of technique failure were equally different between modalities. While the majority of technique failure occurred for medical reasons in PD, the majority of HHD patients experienced technique failure due to social reasons or inadequate resources.

When comparing technique survival between both modalities, the beneficial association with HHD was only apparent after the first year of dialysis. While the highest rates of technique failure were seen during the first year of therapy for both HHD and PD, there was a sharp decrease in failure

rates subsequent to that for HHD patients while the decrease was not as pronounced among PD patients. These different trajectories may be explained by the different nature of the home dialysis modalities. Indeed, the technical complexity of HHD including machine set-up, self-cannulation and adjustments of hemodialysis parameters may contribute to the initial high rates of technique failure. However, it appears that, once established on the therapy, risk of discontinuation is subsequently much lower. In contrast, while PD may be less technically complex, PD-related clinical complications may occur over time leading patients to discontinue the therapy. Such examples include: the progressive loss of residual kidney function and/or peritoneal membrane dysfunction leading to issues with fluid management and clearance or the occurrence of PD-associated peritonitis.

Determinants of technique failure were also significantly different between both modalities, with the major distinctions seen among older patients and by era of treatment. In fact, we demonstrated that the superior technique survival associated with HHD relative to PD was less pronounced in more recent years and among older patients. The increasing utilization of assisted PD in Canada may contribute to better technique survival with PD in patients >65 years old. Moreover, it may also be possible that older patients choose to remain on PD even if they develop a PD-related complication. Our results are consistent with a previous study by Lim et al. examining Australia and New Zealand Dialysis Registry data that showed that elderly patients (≥65 years) had a lower risk of technique failure compared with younger patients (<50 years) and with a study by Lobbedez et al. using the French Peritoneal Dialysis Registry that showed superior technique survival with assisted PD compared to self-care PD.[10,11]

Technique failure rates have also evolved with time with increasing rates with HHD while more stable rates are seen with PD. These trends over time are consistent with previously published reports and are likely related to evolving patient characteristics, different practice patterns and changing criteria for selection. [12,13] With significant growth of HHD in Canada in recent years, increasing rates of technique failure may be related to less strict selection criteria with patients with a higher degree of comorbidity being considered for HHD. Indeed, in a previous analysis of CORR, Perl et al. demonstrated significant differences in patient characteristics in more recent cohorts compared to previous cohorts with increasing age, more diabetes and cardiovascular comorbidity.[12] In contrast, the grossly unchanged rates of technique failure with PD may be attributable to a counterbalance between the selection of older patients with more comorbidities which is associated with a higher risk of failure, and significant reductions PD-related infectious complications over time and the use of assisted PD which are associated with a lower risk.[11,14-16]

Our observed technique failure rates are different compared to previous published reports. For HHD, our 1-year rates of 17% are lower compared to 25% in a recent study from the United States.[2] By comparison, studies from Australia have demonstrated much lower 1-year technique failure rates of 10%.[17] In contrast, our rates in PD at 1 year of 18% are similar to previously published reports. Indeed, rates during the first year have been described at 15-20% but rates as low as 4.9% have also been reported.[3,5,6,18-20] Differences in technique failure rates are likely related to case-mix differences between patients in various countries and centers as well as center-specific practices. These include: quality of pre-dialysis education, training approach, training duration, frequency of follow-up care, nurse-to-patient ratios, and availability of psychosocial support in case of patient or caregiver burnout. These factors are crucial to optimize in order to maintain

patients on home dialysis, but are very difficult to examine using retrospective observational data. Indeed, a very important factor to consider is the differences in training practices. For example, in Australia and New Zealand where technique failure rates are the lowest in HHD, training can be up to 12-16 weeks.[21] Comparatively, training is typically shorter in the United States at 3-6 weeks.[21]

Center experience with home dialysis appears to be an important predictor of technique success. We demonstrated that facility size was a significant determinant of technique survival for both HHD and PD with larger centers having lower rates of technique failure, which is consistent with previous reports.[12,20,22,23] In a recent study of PD patients using data from the Australia and New Zealand Dialysis and Transplant Registry, center-specific factors such as center size, proportion of patients on PD and proportion of patients achieving target phosphate levels were significantly associated with technique failure.[22] These findings may reflect the degree of experience managing home dialysis patients in addition to the availability of support and resources. Nevertheless, these results highlight that there are potentially modifiable practices that may improve technique survival and further research is needed.

Our findings also add to previous reports examining technique survival among home dialysis patients by evaluating the likelihood of returning to PD or HHD after transfer to another dialysis modality. We found that the proportion of patients returning to their initial home modality within 12 months was overall higher in HHD compared to PD. This difference was largest when using a 30-days definition (9.4% for PD and 16.0% for HHD), but became much smaller with definitions of 60 days, 90 days and 180 days.

This study needs to be interpreted in the context of the observational study design and several limitations should be noted. The use of a large administrative database is subject to limitations arising from data validity and missing data elements. Furthermore, details regarding training, center-specific experience with home dialysis, socioeconomic factors and eligibility for both therapies were not available and likely would have been informative. Information regarding who who was performing dialysis at home (patient, caregiver, home-assisted, etc…) was also not available. Additionally, the exact causes of discontinuation were unknown in a subset of patients and would have helped provide a better clinical picture. Lastly, data from the province of Quebec was excluded due to the need for additional ethics and data permissions. Notwithstanding these limitations, we did study a large multicenter cohort of home dialysis patients with extensive adjustment for comorbid conditions and long follow-up period. To our knowledge, this study is the first to comprehensively compare patterns of technique survival between PD and HHD in a large multicenter cohort.

In this large multi-center Canadian study of home dialysis patients, causes and patterns of technique survival differed significantly between PD and HHD patients. Given the distinct nature of these two modalities in addition to the significant differences in patterns of technique survival, future research should move away from direct technique survival comparisons and instead focus on strategies to improve the retention across all home-based dialysis modalities and allow patients to maintain maximal quality of life on the modality of their choosing.

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Legend to Figures

Figure 1: Crude rates of technique failure by time from dialysis initiation in home hemodialysis and peritoneal dialysis

Figure 2: Unadjusted technique survival comparison between home hemodialysis and peritoneal dialysis in Canada 2000-2012

Figure 3: Crude rates of technique failure over time in home hemodialysis and peritoneal dialysis

Figure 4: Adjusted hazard ratios of technique failure comparing home hemodialysis with peritoneal dialysis in specific patient subgroups
Reference group: PD

Table 1: Patient characteristics at home dialysis initiation, 2000 to 2012

	Peritoneal Dialysis	Home Hemodialysis
N	14 461	853
Age, %		
<50 years	23	36
50-65 years	31	41
≥65 years	46	23
Male gender, %	59	67
Race, %		
Caucasian	68	72
Asian	9	6
Black	4	7
Other	20	14
Cause of ESKD, %		
Diabetes	36	28
Glomerulonephritis	19	23
Renal Vascular Disease	18	11
Polycystic Kidney Disease	5	13
Other	19	23
Unknown	3	2
BMI category, %		
< 18.5 kg/m^2	3	3
18.5 - 24.9 kg/m^2	35	28
25 - 29.9 kg/m^2	32	26
> 30 kg/m^2	23	34
Unknown	7	9
Comorbidity Conditions, %		
Diabetes	8	10
Coronary artery disease	24	19
Cerebrovascular disease	10	6
Peripheral artery disease	13	8
Smoker	12	11
Malignancy	8	10
Lung disease	6	1
Region, %		
Atlantic	9	3
Ontario	50	69

West/Prairie	41	28
Facility size*, %		
Small	48	52
Large	52	48
Referral to nephrology, %		
Late referral (< 90-days)	16	19
Referral to nephrology, days (median, IQR)	600 (159-1518)	851 (144-2166)
Era, %		
2000-2004	35	14
2005-2008	32	31
2009-2012	33	55
Access type at initiation of dialysis, %		
Arteriovenous fistula/graft	n/a	39
Central venous catheter	n/a	32
Unknown	n/a	29
Time of starting therapy, %		
Incident	72	22
< 3-months	14	28
3-6 months	8	23
6-12 months	6	27
Prior IHD	27	74
PD type, %		
CAPD	71	n/a
APD	29	n/a
HHD type, %		
Conventional	n/a	52
Short daily	n/a	14
Slow nocturnal	n/a	34

BMI, body mass index; IHD, in-center hemodialysis; PD, peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; APD, automated peritoneal dialysis; HHD, home hemodialysis

***** Facility size definition:
PD: small (<30 new patients per year) and large (≥30 new patients per year)
HHD: small (<5 new patients per year) and large (≥5 new patients per year)

Table 2: Adjusted hazard ratios for technique failure comparing home hemodialysis with peritoneal dialysis

	HR (95% CI) HHD:PD (Reference group: PD)
Unadjusted competing risk model	
Overall	0.81 (0.71-0.92)
Year 1	1.13 (0.95-1.34)
Year 2	0.47 (0.34-0.65)
Year 3	0.58 (0.41-0.82)
Year 4	0.34 (0.18-0.61)
>4 years	0.75 (0.53-1.05)
Multivariate adjusted competing risk model*	
Overall	0.79 (0.69-0.90)
Year 1	1.13 (0.94-1.36)
Year 2	0.46 (0.33-0.65)
Year 3	0.51 (0.35-0.75)
Year 4	0.30 (0.16-0.55)
>4 years	0.65 (0.45-0.94)
Propensity-matched model	
Overall	0.77 (0.65-0.91)
Year 1	1.01 (0.79-1.28)
Year 2	0.44 (0.29-0.66)
Year 3	0.50 (0.32-0.79)
Year 4	0.28 (0.14-0.55)
>4 years	0.95 (0.54-1.67)

HR, hazard ratio; HHD, home hemodialysis; PD, peritoneal dialysis

* Adjusted for age, gender, race, BMI, cause of ESKD, comorbidities, smoking status, facility size and era.

Table 3: Association of patient characteristics with technique failure

	Peritoneal Dialysis		Home Hemodialysis	
	AHR (95% CI)	**P value**	**AHR (95% CI)**	**P value**
Age				
<50 years	1 (Reference)		1 (Reference)	
50-65 years	1.04 (0.96-1.12)	0.39	1.04 (0.78-1.40)	0.77
≥65 years	0.99 (0.91-1.08)	0.83	1.91 (1.37-2.65)	<0.001
Male gender	1.08 (1.02-1.15)	0.01	1.14 (0.88-1.47)	0.31
Race, %				
Caucasian	1 (Reference)		1 (Reference)	
Asian	0.90 (0.80-1.01)	0.07	0.84 (0.50-1.39)	0.50
Black	1.32 (1.15-1.52)	<0.001	1.76 (1.12-2.74)	0.01
Other	1.06 (0.98-1.14)	0.15	1.48 (1.09-2.02)	0.01
Cause of ESKD				
Diabetes	1 (Reference)		1 (Reference)	
Glomerulonephritis	0.92 (0.84-1.00)	0.05	0.79 (0.57-1.10)	0.16
Renal Vascular Disease	0.91 (0.83-0.99)	0.03	1.18 (0.82-1.70)	0.38
Polycystic Kidney Disease	0.98 (0.87-1.12)	0.82	0.61 (0.38-0.97)	0.04
Other	0.88 (0.80-0.96)	0.005	0.67 (0.47-0.97)	0.03
BMI category				
< 18.5 kg/m^2	1.06 (0.87-1.29)	0.58	1.13 (0.49-2.60)	0.78
18.5 - 24.9 kg/m^2	1 (Reference)		1 (Reference)	
25 - 29.9 kg/m^2	1.17 (1.09-1.26)	<0.001	1.30 (0.93-1.81)	0.12
> 30 kg/m^2	1.42 (1.31-1.53)	<0.001	1.65 (1.23-2.23)	0.001
Comorbidity Conditions				
Diabetes	1.08 (0.96-1.21)	0.20	1.24 (0.81-1.90)	0.32
Coronary artery disease	0.95 (0.88-1.02)	0.16	0.77 (0.55-1.08)	0.13
Cerebrovascular disease	0.95(0.85-1.05)	0.30	1.10 (0.69-1.75)	0.68
Peripheral artery disease	0.96 (0.87-1.06)	0.44	1.21 (0.82-1.80)	0.33
Smoker	1.14 (1.05-1.24)	0.002	1.47 (1.01-2.14)	0.04
Facility size*				

Small	1 (Reference)		1 (Reference)	
Large	0.89 (0.84-0.95)	<0.001	0.74 (0.58-0.93)	0.01
Referral to nephrology				
Late referral (< 90-days)	0.98 (0.90-1.06)	0.57	1.14 (0.94-1.55)	0.40
Era				
2000-2004	1 (Reference)		1 (Reference)	
2005-2008	0.99 (0.93-1.06)	0.76	1.22 (0.80-1.86)	0.35
2009-2012	0.88 (0.82-0.95)	0.001	1.56 (1.05-2.32)	0.02
PD type				
CAPD	1 (Reference)		n/a	
APD	1.01 (0.95-1.08)	0.77	n/a	
HHD type				
Conventional	n/a		1 (Reference)	
Nocturnal	n/a		0.83 (0.58-1.17)	0.28
Short-daily	n/a		0.87 (0.67-1.13)	0.30

ESKD, end-stage kidney disease; BMI, body mass index; PD, peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; APD, automated peritoneal dialysis; HHD, home hemodialysis

* Facility size definition:
PD: small (<30 new patients per year) and large (≥30 new patients per year)
HHD: small (<5 new patients per year) and large (≥5 new patients per year)

Table 4: Causes of technique failure in peritoneal dialysis and home hemodialysis patients

Cause	Peritoneal Dialysis (%)	Home Hemodialysis (%)
Peritonitis	13	n/a
Other abdominal complications	7	n/a
Inadequate dialysis	18	6
Social	23	33
Insufficient resources	2	17
Other	28	21
Unknown	9	23

Table 5: Technique failure event rates by different cut-off definitions

	Peritoneal Dialysis			Home Hemodialysis		
	Events	Events / 100 person-year	Proportion returning to PD within 1 year (%)	Events	Events / 100 person-year	Proportion returning to HHD within 1 year (%)
30-days	6066	18.3	9.4%	306	14.9	16.0%
60-days	5874	17.4	6.5%	281	13.3	8.5%
90-days	5729	16.7	4.1%	273	12.8	5.8%
180-days	5569	16.0	1.3%	265	12.3	3.0%
365-days	5494	15.6	n/a	257	11.7	n/a

PD, peritoneal dialysis; HHD, home hemodialysis

Figure 1: Crude rates of technique failure by time from dialysis initiation in home hemodialysis and peritoneal dialysis

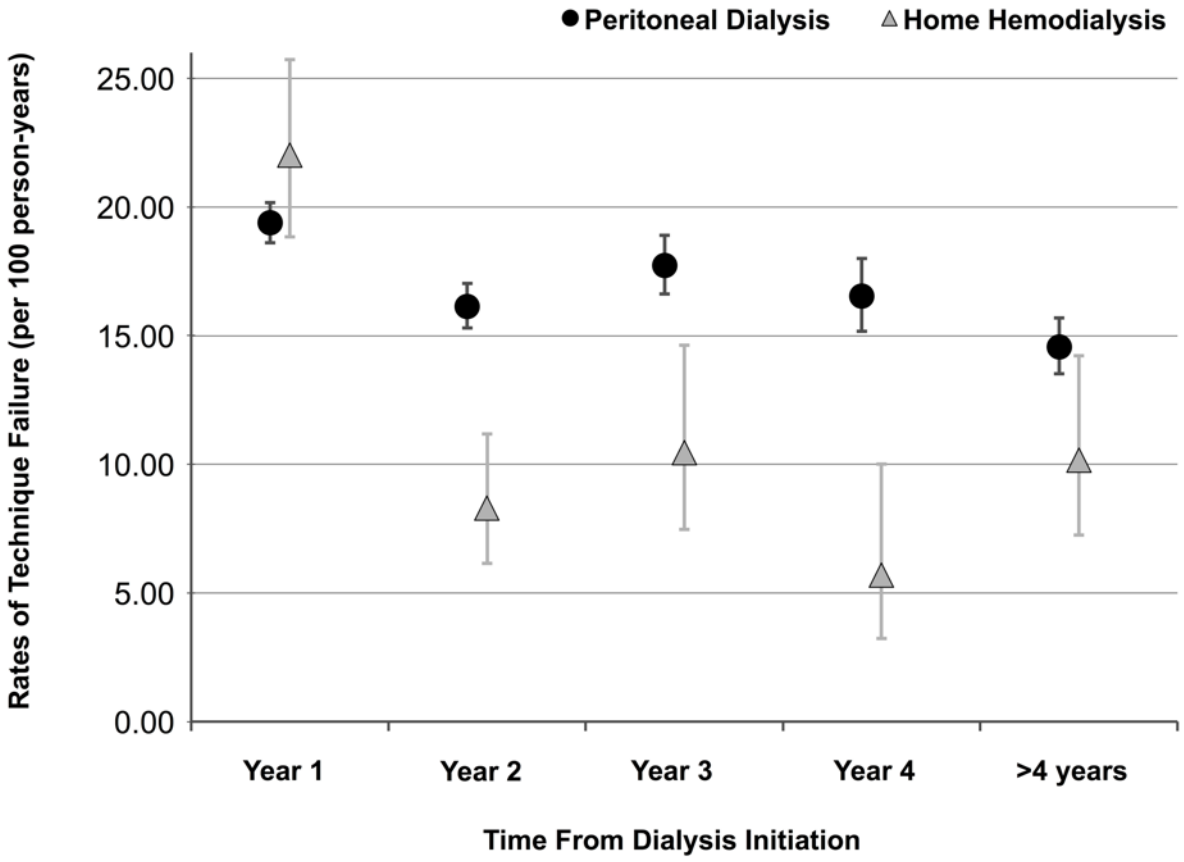


Figure 2: Unadjusted technique survival comparison between home hemodialysis and peritoneal dialysis in Canada 2000-2012

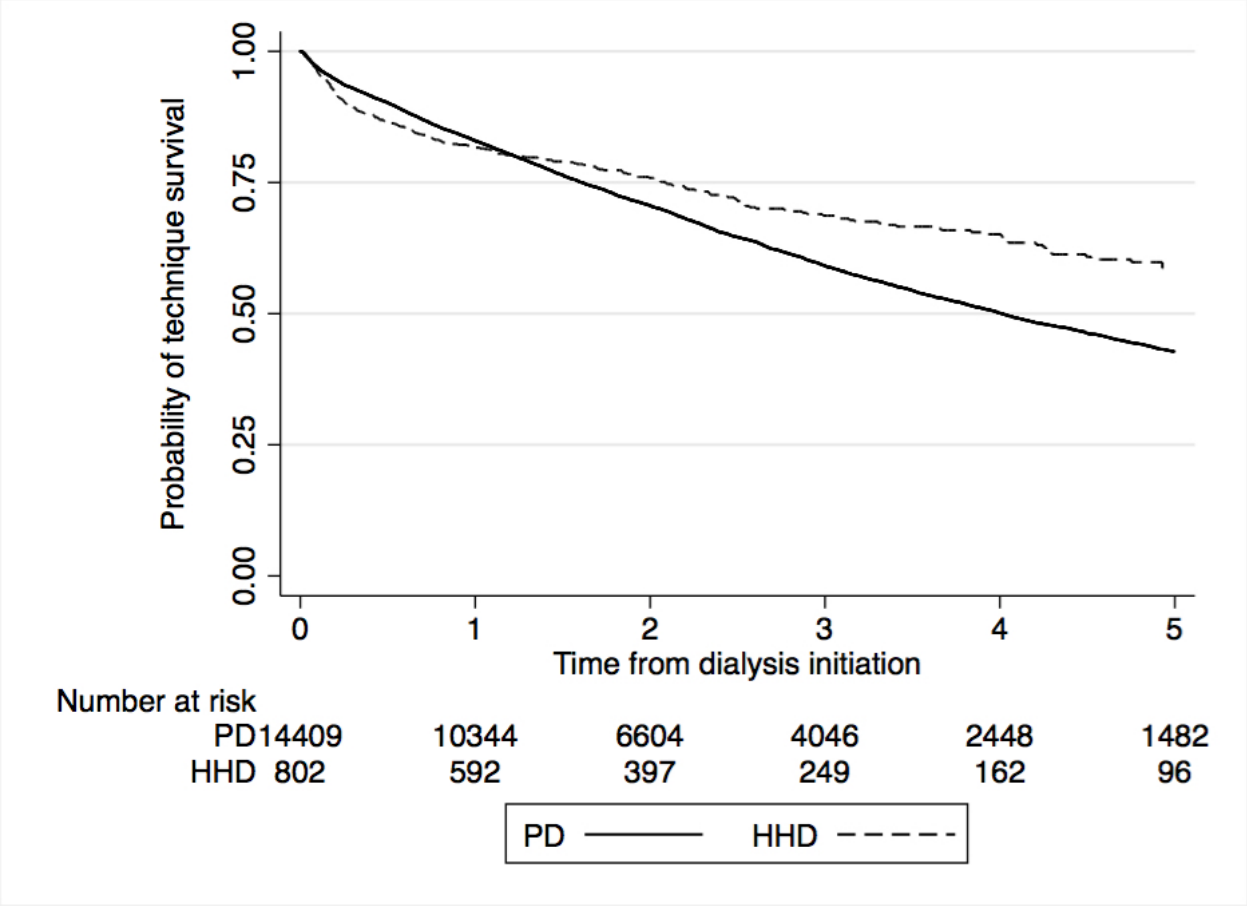


Figure 3: Adjusted hazard ratios of technique failure comparing home hemodialysis with peritoneal dialysis in specific patient subgroups

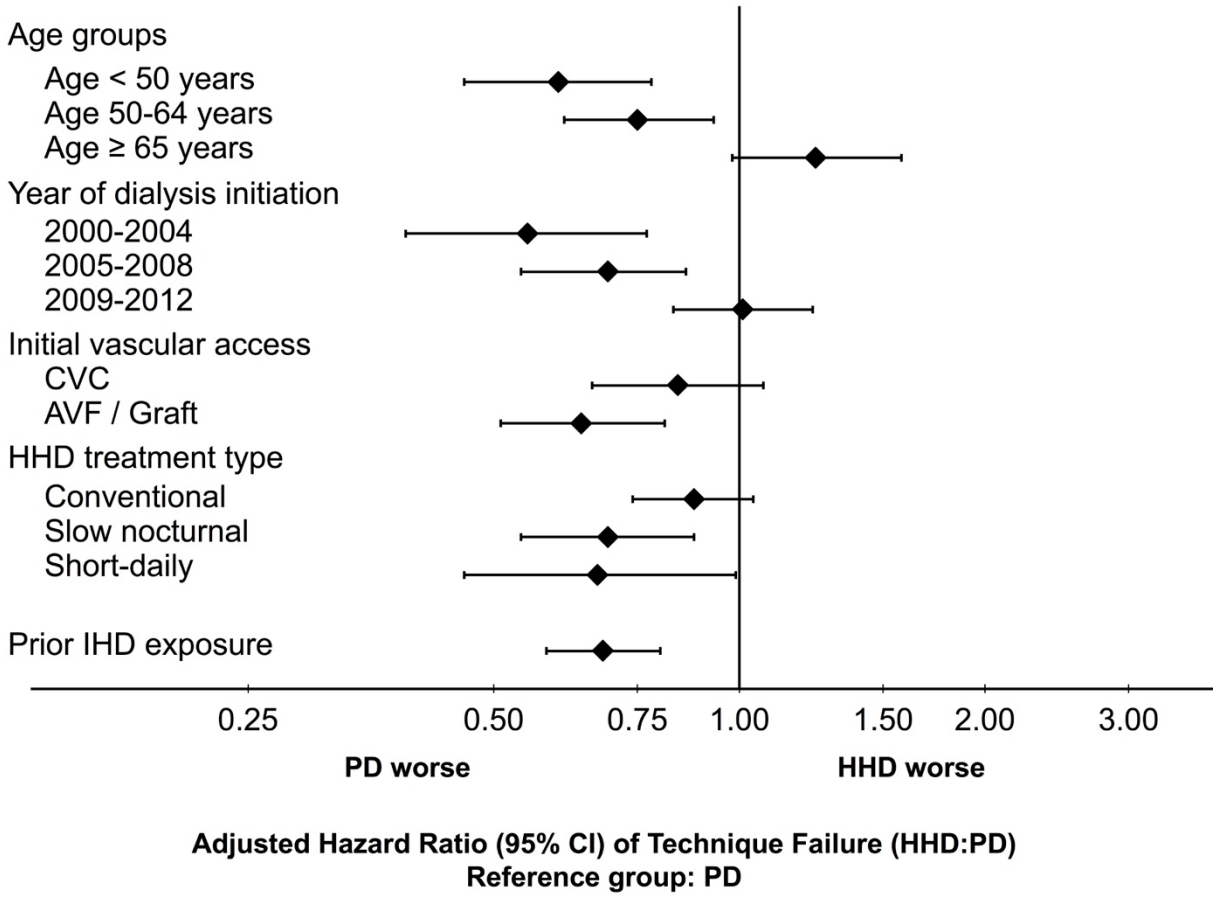
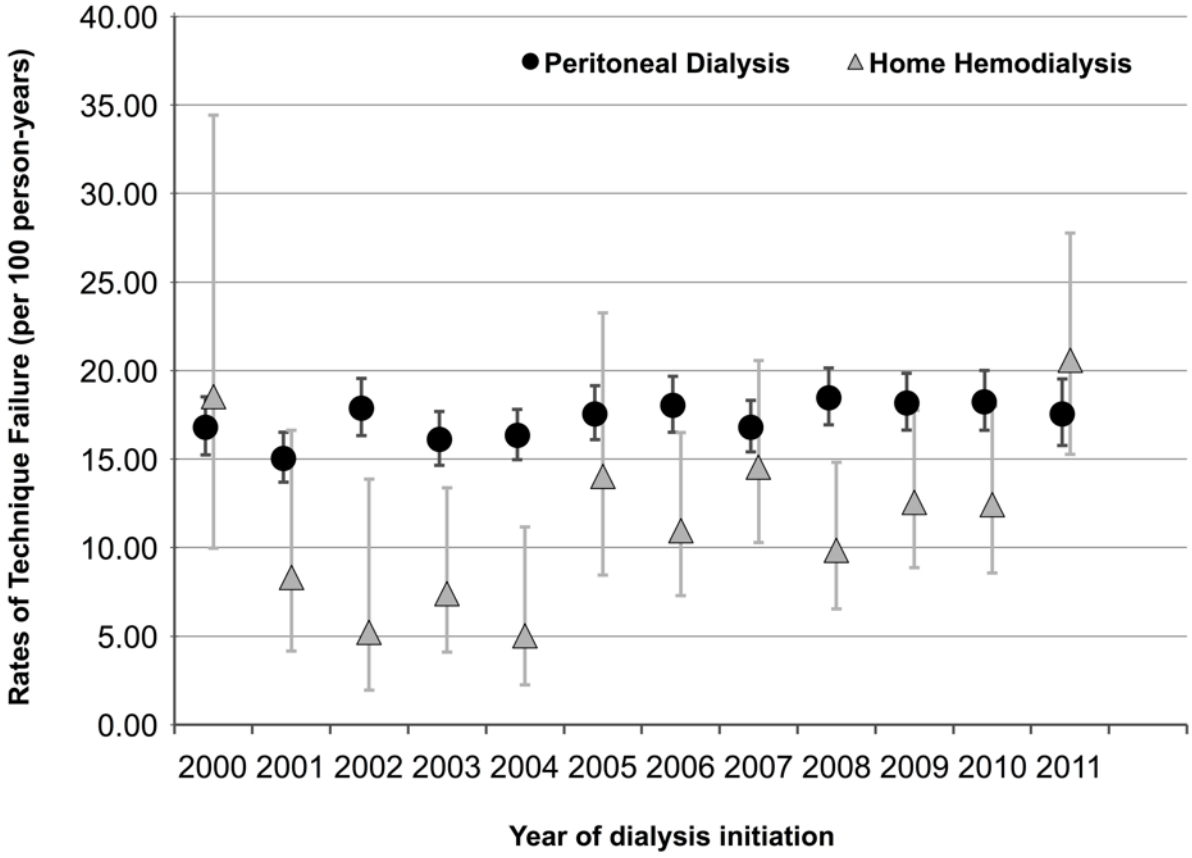


Figure 4: Crude rates of technique failure over time in home hemodialysis and peritoneal dialysis



Supplemental Material

Table S1: Adjusted hazard ratios for technique failure comparing home hemodialysis with peritoneal dialysis in specific patient subgroups

	AHR (95% CI) HHD:PD (reference group: PD)*
Age subgroups	
Age < 50 years	0.60 (0.46-0.78)
Age 50-65 years	0.75 (0.61-0.93)
Age ≥ 65 years	1.24 (0.98-1.58)
Year of dialysis initiation	
2000-2004	0.55 (0.39-0.77)
2005-2008	0.69 (0.54-0.86)
2009-2012	1.01 (0.83-1.23)
Initial vascular access	
Central venous catheter	0.84 (0.66-1.07)
Arteriovenous fistula/graft	0.64 (0.51-0.81)
HHD treatment type	
Conventional	0.88 (0.74-1.04)
Slow nocturnal	0.69 (0.54-0.88)
Short-daily	0.67 (0.46-0.99)
Prior IHD exposure	0.68 (0.58-0.80)

AHR, adjusted hazard ratio; HHD, home hemodialysis; PD, peritoneal dialysis; IHD, in-center hemodialysis

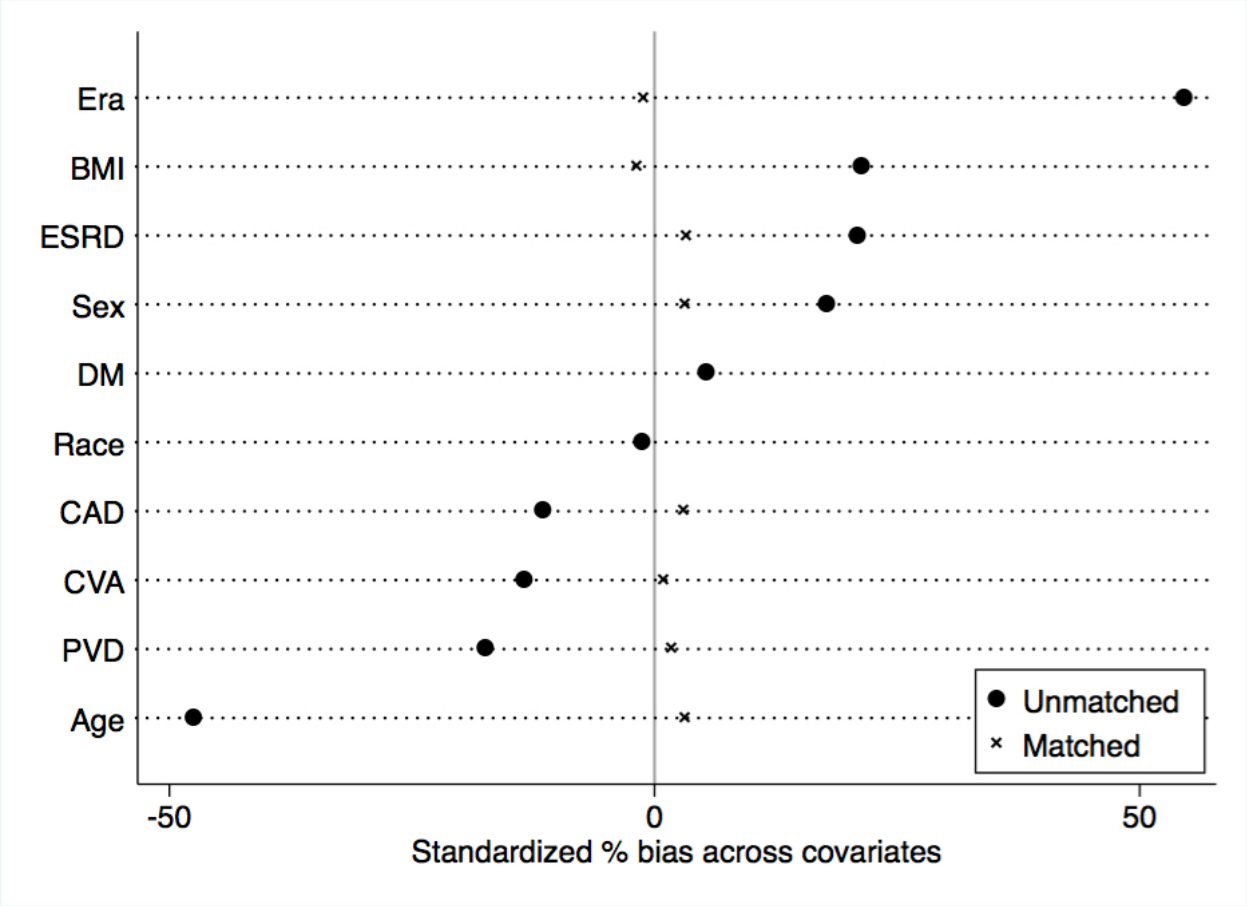
* Adjusted for age, gender, race, BMI, cause of ESKD, comorbidities, smoking status, facility size and era.

Table S2: Adjusted hazard ratios for technique failure comparing home hemodialysis with peritoneal dialysis (90-day technique failure definition)

	HR (95% CI) HHD:PD (reference group: PD)	P value
Multivariate adjusted competing risk model*		
Overall	0.79 (0.69-0.91)	0.001
Year 1	1.14 (0.94-1.38)	0.18
Year 2	0.49 (0.35-0.69)	<0.001
Year 3	0.49 (0.33-0.73)	<0.001
Year 4	0.28 (0.15-0.53)	<0.001
>4 years	0.67 (0.47-0.97)	0.03
Propensity-matched model		
Overall	0.76 (0.64-0.90)	0.002
Year 1	1.01 (0.79-1.29)	0.95
Year 2	0.48 (0.32-0.72)	<0.001
Year 3	0.44 (0.28-0.70)	0.001
Year 4	0.29 (0.14-0.60)	0.001
>4 years	0.84 (0.49-1.43)	0.51

* Adjusted for age, gender, race, BMI, cause of ESRD, comorbidities, smoking status, facility size and era.

Figure S1: Standardized differences before and after propensity-matching



BMI, body mass index; ESRD, end-stage renal disease; DM, diabetes; CAD, coronary artery disease; CVA, cerebrovascular accident; PVD, peripheral vascular disease

Chapter 3: Conclusions

High rates of technique failure remain a challenge and finding strategies to improve technique survival in order to maintain patients on home therapies is of the utmost importance. To increase the prevalent use of home dialysis, not only is it important to increase incident utilization, but it is equally important to maximize home dialysis longevity.

In the first chapter entitled "Technique Survival Home Dialysis: A Review", a literature review identified what is currently known about technique survival in peritoneal dialysis and home hemodialysis, exploring challenges in accurate definitions, and elaborating on complications, reported rates, predictors and causes of technique failure.

The second chapter entitled "A Comparison of Technique Survival in Canadian Peritoneal Dialysis and Home Hemodialysis Patients" is a manuscript that explores differences in patterns and trajectory of technique survival between peritoneal dialysis and home hemodialysis in a retrospective study of a large multicenter Canadian cohort. While home hemodialysis was associated with overall lower technique failure (AHR 0.79, 95% CI 0.69-0.90), comparisons were not proportional over time. In fact, trajectories of technique failure were significantly different between both modalities, which may be explained by the vastly different nature of these modalities. While the highest rates of technique failure were seen during the first year of therapy for both HHD and PD, there was a sharp decrease in failure rates subsequent to that for HHD patients while the decrease was not as pronounced among PD patients. Comparisons also varied among subgroups, especially among different age groups and treatment era. Predictors and causes of technique failure were equally significantly different between these modalities. We also found

that technique failure rates have evolved with time with increasing rates with HHD while more stable rates are seen with PD.

This present thesis has contributed to a more thorough understanding of home dialysis technique survival and is the first study, to our knowledge, to comprehensively compare patterns of technique survival between PD and HHD in a large multicenter cohort. Moving forward, it is imperative to better examine home dialysis technique survival. Given the distinct nature of these two therapies and the significant differences in technique survival patterns, future research should move away from direct comparisons and instead focus on strategies to improve retention across all home-based modalities. This may help allow patients to maintain maximal quality of life on the modality of their choosing.

Future studies should focus on modifiable practices that can help improve technique survival including: 1) optimizing patient selection and recruitment 2) improving patient training practices 3) better understanding of modifiable center-specific practices associated with technique success and associations with clinical outcomes 4) providing adequate resources to support patients at home 5) evaluating optimal frequency of follow-up 6) managing problematic or non-compliant patients and 7) helping to optimize transition to another renal replacement therapy if technique failure unavoidable.