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Long-term prognosis with home hemodialysis

A comparison with other renal replacement therapies

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Long-term prognosis with home hemodialysis

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A comparison with other renal replacement therapies

Helena Rydell



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DOCTORAL DISSERTATION

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Faculty opponent

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Title and subtitle: Long-term prognosis with home hemodialysis. A comparison with other renal replacement therapies.		
<p>Background: The annual mortality for patients on dialysis is high even if it has decreased from 30 % in 1991 to 18 % in 2016. It is mainly caused by an increased cardiovascular and infectious morbidity. Previous studies have reported improved survival for patients with home hemodialysis (HHD). However, patients starting HHD are younger and healthier compared to patients starting other dialysis modalities.</p> <p>The aims of this thesis are to investigate the survival of Swedish patients starting with HHD as initial RRT, to analyse the major non-modifiable factors predicting survival and to study whether there is a benefit beyond patient selection in patient survival, health care utilization and subsequent renal graft survival for patients starting HHD compared with patients starting IHD or PD. An additional aim is to compare the effect on some modifiable risk factors between HHD and IHD.</p> <p>Methods: The studies in this thesis are retrospective observational studies based on data from patient records in study I and II and data from Swedish Renal Registry and the Swedish Inpatient Registry in study III and IV. In study I patients starting HHD at Lund University hospital 1971-1998 were included. In study II patients starting HHD at Lund University hospital 1983-2002 were matched with patients starting IHD at Malmö General Hospital. In study III and IV, all Swedish patients starting HHD during 1991-2012 were matched with patients starting IHD and PD. Matching was performed according to sex, age, Davies Comorbidity Index in study II, Charlson comorbidity index in study III-IV and date of start of dialysis,</p> <p>Results: The annual mortality for patients starting HHD in Lund was 4.9 %. Age, comorbidity and decade of start of HHD had a significant impact on survival. For patients younger than 60 years without comorbidities, subsequent renal transplantations did not have a significant impact on survival. (Study I)</p> <p>Patients starting HHD have a significant superior median survival, 18.5 years, compared with patients starting IHD, 11.9 years, or PD, 15.0 years (Study III). Patients starting HHD have less health care consumption measured as hospital admissions compared with IHD and PD. This advantage is partly caused by less admissions with cardiovascular diagnoses compared IHD and less admissions with infectious disease diagnoses and longer dialysis technique survival compared with PD. (Study IV). There was no significant difference in subsequent renal graft survival after HHD compared to IHD or PD (Study III). Contributing modifiable factors to the improved prognosis for patients on HHD are less prescribed antihypertensives and diuretics, as indirect measures of improved fluid balance, and lower phosphate levels, compared to patients on IHD. (Study II)</p> <p>Conclusion: Patients starting HHD as initial RRT exhibit an improved long-term prognosis beyond differences in patient selection, a superior survival and less health care utilization, compared with patients starting IHD or PD. The results of this thesis are strong incentives for increased use of HHD for patients on maintenance dialysis.</p>		
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A comparison with other renal replacement therapies

Helena Rydell



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Till pappa

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List of Publications

1. Excellent long time survival for Swedish patients starting home-hemodialysis with and without subsequent renal transplantations
Helena Rydell, Lena Krützen, Ole Simonsen, Naomi Clyne, Mårten Segelmark
Hemodialysis International 2013; 17:523–531
2. Home- or Institutional Hemodialysis? – a Matched Pair-Cohort Study Comparing Survival and Some Modifiable Factors Related to Survival
Helena Rydell, Naomi Clyne, Mårten Segelmark
Kidney and Blood Pressure Research 2016; 41:392-401
3. Improved long-term survival with Home Hemodialysis compared with Institutional Hemodialysis and Peritoneal Dialysis - a matched cohort study
Helena Rydell, Kerstin Ivarsson, Martin Almquist, Mårten Segelmark, Naomi Clyne
Submitted
4. Fewer hospitalizations and prolonged technique survival with Home Hemodialysis– a matched cohort study from the Swedish Renal Registry
Helena Rydell, Kerstin Ivarsson, Martin Almquist, Naomi Clyne, Mårten Segelmark
In manuscript

Abbreviations and definitions

ANZDATA	Australia and New Zealand Dialysis and Transplant registry
ATC	Anatomic Therapeutic Chemical classification system (according to WHO)
AV fistula	Arteriovenous fistula
AV graft	Arteriovenous graft fistula
BMI	Body Mass Index
CHD	Conventional hemodialysis (usually defined as 4 hours thrice weekly, but in some studies 3-6 hours 2-4 times weekly)
CKD	Chronic kidney disease
CI	Confidence Interval
DDD	Defined Daily Dose (according to WHO)
DOPPS	Dialysis Outcomes and Practice Pattern Study (an international observational prospective cohort study)
ERA-EDTA	European Renal Association – European Dialysis and Transplant Association (the funder of the European renal registry)
ESA	Erythropoiesis Stimulating Agents
ESRD	End-stage renal disease
GFR	Glomerular Filtration Rate
HD	Hemodialysis (used with a wide definition in this thesis including HDF and hemofiltration, in some other studies only used for diffusive dialysis therapy)
HDF	Hemodiafiltration (convective and diffusive dialysis therapy)
HHD	Home hemodialysis (self-administered hemodialysis performed at home)
HR	Hazard ratio
ICD	International Classification of Diseases (by WHO)
IHD	Institutional hemodialysis (hemodialysis performed at a dialysis clinic)

IQR	Inter-quartile range
Kt/V	Dialysis dose calculated from the clearance of urea (K), the treatment time of the dialysis session (t) and the distribution volume of urea in the body, that is the volume of water (V)
NHD	Nocturnal hemodialysis (nocturnal dialysis sessions between 6 and 10 hours performed 3-6 times weekly)
PD	Peritoneal dialysis
PTH	Parathyroid hormone
RR	Relative Risk
RRF	Residual Renal Function
RRT	Renal Replacement Therapy (dialysis and renal transplantation)
SDHD	Short Daily Hemodialysis (dialysis sessions shorter than 3 hours performed 5-6 times weekly)
SRR	Swedish Renal Registry
USRDS	United States Renal Data System (a renal registry)

Introduction

Historic perspectives

Home hemodialysis

The first patient started hemodialysis at home in Japan 1961[1]. A couple of years later, the first patients started home hemodialysis (HHD) in Boston and in London[1]. In 1971, the first patient started HHD at Lund University hospital[2].

Following these breakthrough treatments, the number of patients with HHD grew fast, at least in the US. Among the 11000 patients on dialysis in the US 1973, 40 % had HHD[3]. However after 1973, when dialysis became financially covered by Medicare, the focus changed from HHD to institutional hemodialysis (IHD). A lot of dialysis units were built and at the same time older and sicker patients were accepted for dialysis. In 1980 4.6 % and in 1992 1.3 % of the US dialysis patients had HHD[3].

Development of hemodialysis

Before the start of HHD, the development of hemodialysis had been in progress since the beginning of the 20th century. Dialysis had been performed in dogs in 1913 by John Abel and with a few attempts in humans by George Haas in 1923. Two decades later, in 1943, the Dutch physician, Willem J Kolff restarted the attempts to treat humans with dialysis[4]. Interestingly, at the same time a Swedish physician, Nils Alwall, developed another hemodialysis device, without knowing about the attempts of Willem J Kolff. The first patient to be treated with dialysis by Nils Alwall in Lund was in 1946[2].

Apart from being one of the pioneers of hemodialysis, Nils Alwall was responsible for two of the major steps which transformed hemodialysis from an exclusively acute treatment to a treatment both for acute and maintenance dialysis. Firstly his hemodialysis device from 1946 was the first with a technique for ultrafiltration. Secondly, he recognized the need for a disposable dialyser and developed the first disposable plate-kidney during the sixties in cooperation with Holger Crafoord, who was the founder of Gambro in Lund[2].

Another important factor affecting the feasibility of maintenance hemodialysis is access to the blood-stream, that must persist for repeated treatments. The development of a Teflon arteriovenous shunt by Belding Schribner in 1960 made frequent dialysis treatments over time possible[3]. After each dialysis session, the needles in the artery and the vein, were not removed but connected by a Teflon shunt until the next dialysis session[2]. In 1966 Michael J Brescia and James E Cimino, took the next developmental step, when they created the endogenous subcutaneous arteriovenous fistula[5].

Development of peritoneal dialysis

The development of peritoneal dialysis (PD) took place in parallel with the development of hemodialysis. In 1923 PD was performed for the first time in humans by Georg Ganter. There was a slow increase in the continued use of PD, due to concerns about complications such as peritonitis and leakage[6]. In the sixties, new improved PD catheters were developed and enabled an increased use of PD with fewer complications. Until 1976, PD was used as an intermittent dialysis treatment in hospitals, after which continuous ambulatory peritoneal dialysis (CAPD) was developed. After the introduction of CAPD, PD became a home dialysis treatment[3].

The growth of maintenance dialysis

In 1957, the only Swedish hemodialysis center was situated in Lund. The second center opened in Umeå in 1958[4]. During the sixties and onwards, gradually, maintenance dialysis became available[2]. In Sweden, during 1972 and 1982, 270 and 890 patients had maintenance dialysis, hemodialysis or peritoneal dialysis[7]. In 2016, the number of patients on maintenance dialysis was around 4000[8].

Prescriptions of maintenance hemodialysis

During the sixties, maintenance hemodialysis was performed with long sessions 20-40 hours weekly. During the following decades, the duration of the dialysis sessions was reduced to 2-4 hours thrice weekly, first in the US subsequent to changes in the reimbursement system, and subsequently also in Europe[9].

Epidemiology

Incidence

The annual number of patients starting renal replacement therapy (RRT) in Sweden rose from 132 in 1970 to 614 in 1985[7]. Since 1997, there has been a stable incidence of around 1100 patients (Figure 1). Expressed as incidence per million, the number of patients increased from 17 per million in 1970, to 106 per million in 1991 and 130 per million in 2006 with a decline to 119 per million in 2016[8, 10].

The incidence is low in Sweden, as well as in the other Nordic countries[10]. This is probably related to a publicly funded health care that is available for the whole population. Other contributing factors are most likely the quality of primary care, well-functioning referral practices and established pre-dialysis care at specialist nephrology clinics. Another important factor is the relatively low incidence of diabetes mellitus[11].

The highest, and still rising incidence of RRT has been reported in Taiwan, the Jalisco region of Mexico, Brunei and the United States with levels between 378 and 476 per million, according to the USRDS[10]. In these countries, the proportion of patients with diabetic nephropathy as primary renal diagnosis among incident ESRD patients was 45-62 % in 2015 (except Brunei, with unknown proportions). In contrast, in Sweden in 2016, the proportion of diabetic nephropathy in incident ESRD patients was 26 % [10].

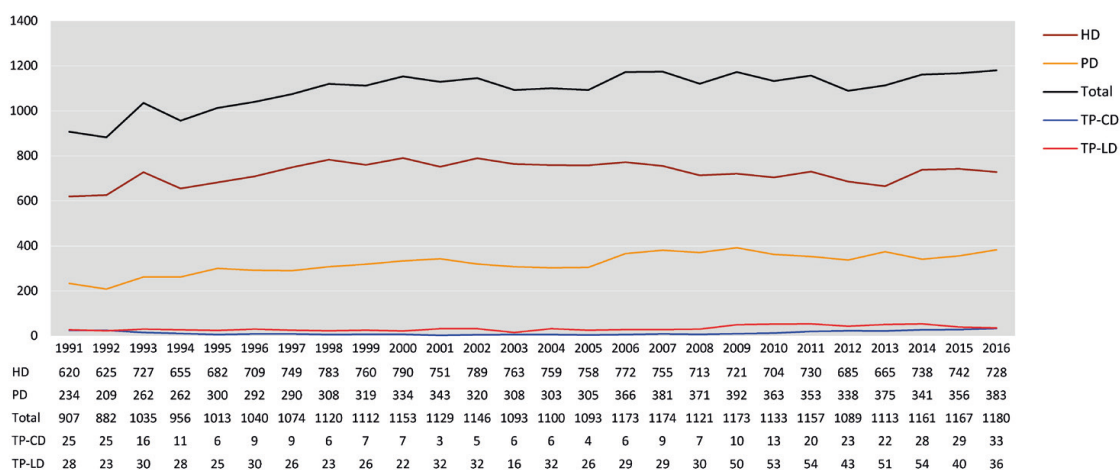


Figure 1
Incident patients with different renal replacement therapies in Sweden during 1991-2016 (SRR)

Prevalence

The number of prevalent patients with RRT in Sweden is still rising, from 3737 in 1990 to 9693 in 2016 (Figure 2). However, for patients on dialysis the prevalence has stabilised around 400 since 2010, but is still rising for patients with renal transplants, from 500 in 2010 to 560 per million in 2016[8]. Most Nordic countries have a similar prevalence of RRT compared with Sweden, although Iceland is an exception, with a lower overall prevalence, 675 per million[10]. The prevalence of RRT is highest, 2000 to 3200 per million, in Taiwan, Japan and the United States, and the numbers are still rising[10].

The increasing prevalence in Sweden, despite a decline in the incidence of RRT, is a reflection of a high rate of renal transplantations[10], with a subsequently improved patient survival compared to dialysis[8]. However, the improved survival for patients on dialysis does also have an impact[8].

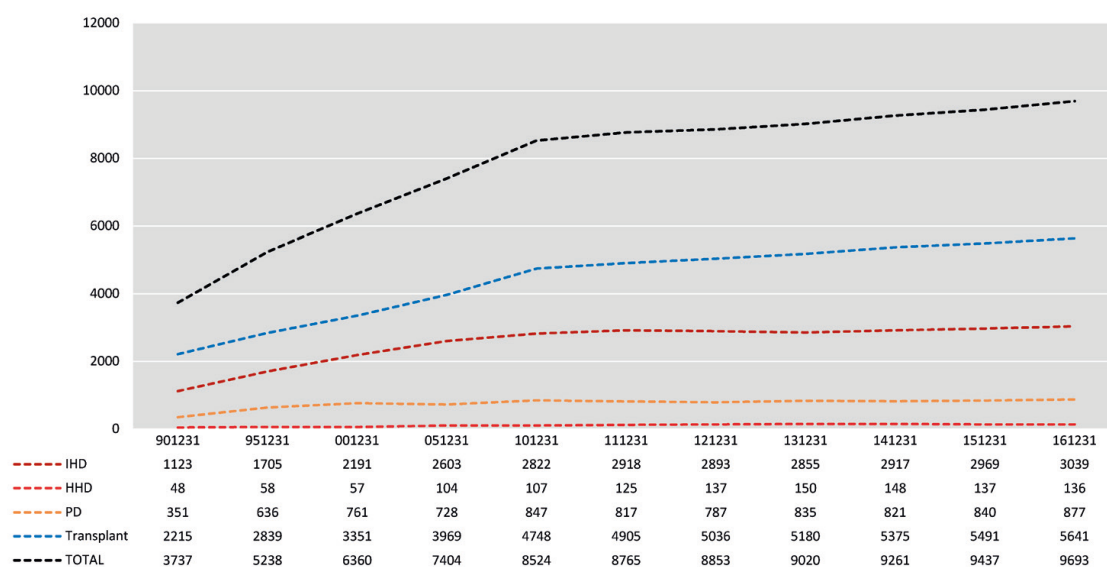


Figure 2
Prevalent patients with different renal replacement therapies in Sweden during 1991-2016 (SRR)

Distribution of different RRT

Among incident patients starting RRT in Sweden 2016, 69 % started with IHD, followed by 34 % who started PD. Renal transplantation and HHD comprised small proportions among incident patients, 6 % and 1 % respectively. This is in contrast to prevalent patients of whom the majority, 58 %, have a functioning renal transplant. Among prevalent patients on dialysis, 75 % had IHD, 22 % had PD and only 3 % had HHD in 2016[8, 12]. The proportions have been stable in Sweden since the nineties but there are substantial differences between countries in the

world. Sweden is among the top ten countries with the highest proportions of transplantation and home dialysis, PD and HHD, among prevalent patients on RRT according to the USRDS[10]. Iceland and Norway have the highest proportions with renal transplantation, with around 70 %, while countries with the lowest proportions have less than 10 %. PD is most common in Hong Kong and the Jalisco Region of Mexico, with 70 % and 51 % of all patients on dialysis respectively. HHD, on the other hand, is most common in New Zealand and Australia with 18 % and 9 % of all patients on dialysis, respectively. In the majority of countries, more than 90 % of all prevalent patients on dialysis have IHD[10].

Patients characteristics

Sex

Although CKD at stages 3-4 is more common among women[12], the majority of patients starting RRT are men. In Sweden, men comprise 64 % of all patients on RRT[8], compared with 62 % in Europe[13], in Australia and in New Zealand[14] and 58 % in the US[10]. To what extent this depends on slower progression of CKD for women is not clear, but inequality in the access to RRT, should also be considered. Female patients registered in the SRR with CKD stages 3-5, have less proteinuria and lower blood pressure, despite fewer prescribed ACE inhibitors or angiotensin receptor blockers, compared with men[8]. In Sweden, GFR at start of dialysis, is lower for women compared with men, 6.1 ml/min compared with 6.5 ml/min[8].

Age

The mean age of Swedish incident patients starting dialysis was 31 years in 1970 and rose gradually to 63 years in 1985[7], after which it has stabilised between 60 and 64 years[8]. The mean age at start of dialysis was 64 years in 2016. The majority of the patients starting RRT in Sweden is above 65 years of age, comprising 57 % of all patients in 2016[8]. This is also the case in Australia and New Zealand with 66 %[14], but in countries reporting to the ERA-EDTA registry[13] and to the USRDS[10], the proportion was lower, with an average age above 65 years in 52 % and 49 % of all patients, respectively.

Comorbidity

Among European patients starting RRT, 70 % have comorbidities as defined by the ERA-EDTA registry; comprising cardiovascular comorbidities, diabetes mellitus and/or malignancies[15]. Among incident patients in Sweden, only 60% have comorbidities[15]. This could, however to at least to some extent, be due to

differences in how cardiovascular comorbidities are registered in the SRR and other national registries.

Diabetes mellitus is the most common comorbidity in incident patients, comprising 38 % in Sweden and 40 % in patients registered in the ERA-EDTA. It is followed by ischemic heart disease in 23 % of the Swedish patients and 25 % of the patients in the ERA-EDTA registry[15]. The ANZDATA does also reports diabetes mellitus as the most common comorbidity followed by ischemic heart disease[14], while the USRDS does not report comorbidities[10].

Renal diagnosis

Among incident patients starting RRT in Sweden, diabetic nephropathy is the most common renal diagnosis. This is the cause of the end-stage renal failure in 26 % of the patients, and is then followed by adult polycystic kidney disease, glomerulonephritis and hypertension[8]. Diabetic nephropathy is the most common diagnosis for patients registered in the ERA-EDTA[13], the ANZDATA[14] and in the USRDS[10], and is followed by hypertension in the US and glomerulonephritis in Europe, Australia and New Zealand.

Among prevalent patients in Sweden, glomerulonephritis is the most common diagnosis, comprising 25 % of all patients, and followed by diabetic nephropathy, comprising 18 %[8]. The ERA-EDTA registry[13] and the ANZDATA[14] report the same order of the diagnoses, while the USRDS[10], reports diabetic nephropathy in 38 % of prevalent patients followed by hypertension. Thus, in the US, both among incident and prevalent patients, the high prevalence of the metabolic syndrome in the general population, is reflected in the distribution of renal diagnoses among patients with RRT[16].

Mortality

Annual mortality

Although annual mortality, for all patients with RRT in Sweden has decreased from 13.8 % in 1991 to 9.2 % in 2016, it remains high[8]. This is primarily due to an improved survival for dialysis patients, who had an annual mortality of 30 % in 1991 which decreased to 18 % in 2016 (Figure 3). The annual mortality for patients with renal transplants in Sweden was around 3 % in the beginning of the 1990s and decreased to around 2.5 % in the new millenium. Other renal registries, ERA-EDTA[13], USRDS[10] and ANZDATA[14]. have reported similar improvement in survival, both for patients on dialysis and with renal transplants, during these decades.

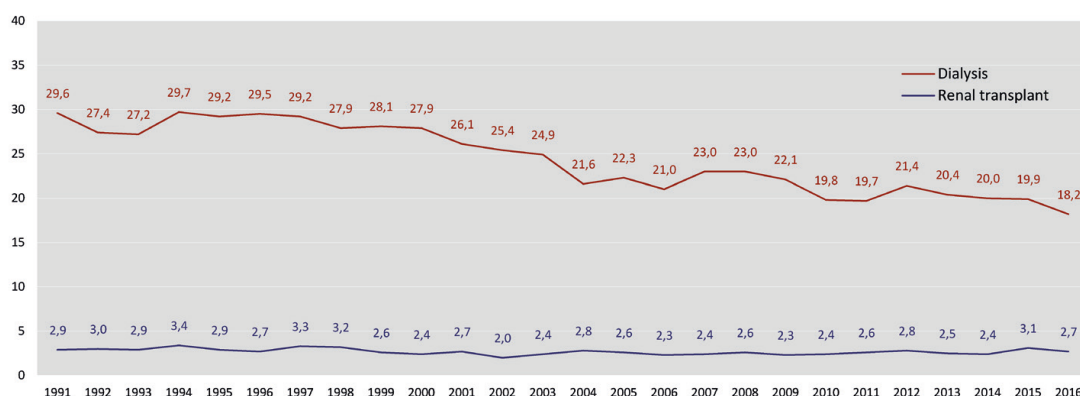


Figure 3
Annual mortality for patients with renal transplants and dialysis in Sweden 1991-2016 (SRR)

Mortality compared with other diseases

Despite improvement, the mortality for patients with RRT, is high compared with the general population and with patients with other chronic diseases[10, 17]. In the United States the expected remaining lifetime for patients younger than 80 years with dialysis is less than one third of that of the general population. For patients with renal transplants, who are younger than 75 years, the expected remaining lifetime is longer, but still only 68-84 % of that of the general population[10]. For European patients, the age-standardized cardiovascular and non-cardiovascular mortality have been reported as 8.8 and 8.1 times, respectively, higher for dialysis patients compared with the general population[17].

In comparisons with patients older than 65 years, covered by Medicare in the US, the mortality rate for patients of that age on dialysis, was 1.7 times higher compared with patients with heart failure and more than twice as high compared with patients with cancer or cerebrovascular disease[10].

Causes of death

All RRT

Cardiovascular disease is the most common cause of death for patients with RRT, according to the SRR[8], the ERA-EDTA registry[17] and the USRDS[10]. The ANZDATA registry reports cardiovascular disease as the most common cause of death for patients on dialysis, while malignancies are the most common cause for patients with renal transplants[14].

However, the causes of death for the majority of patients with RRT in Europe[13], Australia and New Zealand[14] are non-cardiovascular, a development during recent years during which the proportion of cardiovascular deaths has declined. According to the SRR, cardiovascular disease was the cause of death for 50-60 % of all patients on RRT in the nineties, but has decreased to 40-45 % after 2010[8]. In the US, the proportion of cardiovascular diseases among causes of death for patients with renal transplants is similar to what is reported in Europe, while the proportion among patients on dialysis is still above 50 %[10].

Patients on dialysis

After cardiovascular disease, the second most important cause of death for patients on dialysis in Sweden is infectious diseases, which has increased from 10-15 % during the nineties and comprises around 20 % of all deaths since 2000[8]. For patients on dialysis and included in the ERA-EDTA[18], the USRDS[10] and the ANZDATA registries[14], infectious diseases have also been reported as the second most important cause of death[18].

Patients with renal transplants

For patients with renal transplants the causes of death are divergent between countries and continents. In Europe and in the US, cardiovascular disease is the most common cause of death. In the US, this is followed by both infectious diseases and malignancies, which are equally common[10]. Data from the ERA-EDTA registry show that infectious diseases are the second most common cause[18], while data separately from Sweden show that malignancy is the second most common cause of death[8]. In Australia and New Zealand, malignancies are even more common than cardiovascular disease[14].

Reasons behind the increased mortality in patients with RRT

Although cardiovascular disease is the most common cause of death in most populations of patients with RRT, it only partly explains the increased mortality for patients with RRT. For patients on dialysis included in the ERA-EDTA registry, the cardiovascular and the non-cardiovascular mortality rates were 43 per 1000 person years and 57 per person years, respectively, compared with 5 and 7 per person years for the general population[17].

Infectious diseases emerges as a more important cause than malignancies behind the increased mortality risk compared with the general population, both patients on dialysis and with renal transplants. Vogelzang et al used data from the ERA-EDTA registry and showed that infection-related mortality was 82 times higher in dialysis patients and 32 times higher for transplant patients compared with the general population. Malignancy-related mortality was increased, albeit to a lower extent, 2,9 times for dialysis and 1.7 for transplant patients, respectively[18].

Hospital admissions and causes of morbidity

According to the USRDS, patients with ESRD are admitted to hospital on average twice yearly. The figures declined between 2006 and 2015 from 2.1 to 1.7 per patient year for patients on HD, from 2.1 to 1.7 for patients on PD and from 1.0 to 0.8 for patients with renal transplants[10]. The European DOPPS study reported lower admission rates for hemodialysis patients, who were admitted to hospital on average once yearly during 1998-2000[19].

Causes of admissions

According to the European part of the DOPPS study, cardiovascular disease was the most common cause of admissions during the period 1998-2002[19]. According to the USRDS, cardiovascular disease and infectious diseases account for 50 % of all admissions, for patients with RRT [10]. Cardiovascular disease was the most common cause of admissions for patients with RRT during 2006 to 2012, and when analysed separately for patients with HD. For patients on PD or with a renal transplant, infectious diseases were slightly more common than cardiovascular diseases. However, after 2012, the proportion of admissions due to cardiovascular disease decreased to the same level as for infectious diseases for all patients with RRT[10].

Cardiovascular diagnoses

According to the Peer Kidney Care Initiative report 2014, based on data from the USRDS, the most common cardiovascular diagnoses for admissions for patients on dialysis, were heart failure and fluid overload, followed subsequently by cardiac arrhythmia, acute coronary syndrome and stroke[20]. The annual admission rates with heart failure and fluid overload as primary diagnoses were 21 and 18 per 100 patient-years for incident and prevalent patients respectively, while the annual rates for the other diagnoses were lower, between 2 and 6 per 100 patient-years[20].

Infectious disease diagnoses

According to the same report, the most common infectious diseases for patients on dialysis, were sepsis or bacteremia and dialysis-access related infections, including peritonitis[20]. All these diagnoses were more common among incident compared with prevalent patients, probably related to a higher incidence of dialysis catheters in incident hemodialysis patients.

Modifiable risk factors associated with hemodialysis treatment

Dialysis accesses, dialysis doses and patient education are factors prescribed by health care personnel and which all have an impact on the prognosis for patients on hemodialysis.

Dialysis accesses

Association with survival

Observational studies have shown a worse survival for patients starting IHD or HHD with intravenous dialysis catheters compared with patients who start with AV fistulas or AV grafts[21-25]. In addition, the DOPPS study[21] and a large study based on data from the USRDS[23], reported a more pronounced advantage for AV fistulas than for AV grafts. The worse survival for patients with dialysis catheters is reflected in a higher risk of hospitalizations compared to AV fistulas for patients with IHD[26] as well as for HHD patients [22] In the DOPPS study, there were no significant differences in the risk of hospitalization between patient with an AV graft or an AV fistula[26].

Confounding by patient selection or causative association?

Although several observational studies have shown an association between different types of dialysis accesses and patient survival and hospitalizations, the question still remains; is the association causative or just a reflection of differences in the selection of patients for different types of accesses? The creation of fistulas is often more complicated in older patients especially if they have several comorbidities.

There are some studies, which show differences beyond patient selection. Hicks et al reported a superior survival for patients with AV fistulas compared with intravenous dialysis catheters or AV grafts which persisted in all age groups. However, the advantage for AV grafts compared with dialysis catheters only persisted in patients between 49 and 89 years and not for the youngest or oldest patients[23]. In another study, incident and prevalent patients with dialysis and with an urgent need of a permanent dialysis access, were randomized to either early cannulation AV grafts or tunneled dialysis catheters. After 6 months of follow up, patients with AV grafts had lower mortality (5 % compared with 16 %) and fewer episodes of bacteremia (3 % compared with 16 %)[27].

Possible mechanisms behind differences in survival

There are other studies analysing possible mechanisms behind the increased mortality and morbidity for patients with intravenous dialysis catheters.

Data from the DOPPS study showed an increased frequency of hospital admissions with cardiovascular and infectious diagnoses and with problems directly related to the vascular accesses for patients with dialysis catheters compared with AV fistulas or AV grafts, after statistical adjustment for age, sex, BMI and a number of comorbidities[26].

In an observational study by Hayes et al, with inclusion of patients on HHD, the time to first bacteremia was shorter for patients with a dialysis catheter compared with an AV fistula or AV graft[28]. The most common bacteria were coagulase-negative staphylococci followed by staphylococcus aureus, in fact gram-positive bacteria, which commonly are transmitted through cannulation and catheters.

However, in another study based on data from the DOPPS study, the interactions between access type, mortality and access complications were further analysed[21]. In that study, dialysis catheters were significantly associated with increased mortality and increased risk of non-infectious and infectious (local and systemic) access complications compared with AV fistulas. All these factors were included in the same multivariable cox regression model. In the multivariable analysis, the hazard ratios were nearly identical with the univariable analyses of the interactions between access type and survival or access type and access complications, respectively. A reasonable interpretation of these results, might be that access-related complications per se are not responsible for the association between access type and survival. Even though several studies have shown a worse prognosis for patients with dialysis catheters, the explanations behind the differences between dialysis access types are still not fully elucidated.

Dialysis dose

Adequate dialysis dose has previously mainly been assessed as the clearance of small molecules, measured as Kt/V. Kt/V is calculated using the clearance of urea (K), which is used as a marker of small molecules, the treatment time of the dialysis session (t) and the distribution volume of urea (V) in the body, that is the volume of water. A higher Kt/V can be obtained by increasing blood- and dialysate flow rates and by increasing treatment time. The current international KDOQI (Kidney Disease Outcomes Quality Initiative) guidelines recommend a minimum Kt/V of 1.2 for conventional hemodialysis, i.e. four hours thrice weekly.

However, with rising awareness of the importance of fluid removal and other uremic toxins, such as phosphate, with a clearance different from urea, there has

been a growing trend towards longer or more frequent dialysis sessions. As larger molecules than urea have a slower movement between compartments within the body and over the dialysis membrane, time on dialysis is the crucial factor. In consequence, Kt/V is a poor measure of the dialysis adequacy in terms of such molecules.

Impact of dialysis dose measured as Kt/V

There are several registry studies, mostly from the US, showing an improved survival with increased dialysis dose expressed as Kt/V for patients with hemodialysis thrice weekly[29-33]. On the other hand, some studies report a threshold between 1.3 and 2.4 after which there is no further reduction of the risk[30-32], in fact a paradoxical increase has been reported above these levels [32, 34]. Deeper analyses of this paradoxically increased mortality risk, have found an association with malnutrition. Patients with severe malnutrition and a worse prognosis have a low V and can therefore more easily achieve a higher Kt/V[34, 35].

The HEMO study, the to date only randomized controlled study, compared two different Kt/V goals: 1.25 or 1.65 for patients with thrice weekly IHD. This study failed to show any significant differences in survival between the two Kt/V groups[36]. However, in a secondary analysis, based on the achieved Kt/V rather than the Kt/V goal, a significantly improved survival was reported with higher Kt/V. In this analysis, another formula for Kt/V was used, which considered the rebound of urea from the extracellular to the intravascular compartment (eKt/V). In the low-dose group, each 0.10 lower eKt/V compared with the group median of 1.14 was associated with a 58 % increased risk (relative risk 1.58) of mortality. For the high-dose group, each 0.10 lower eKt/V compared with the group median of 1.14 was associated with a 37 % increased risk (relative risk 1.37) of mortality[37].

In a prespecified subgroup analysis on sex differences in the HEMO study, women in the high-dose group had a 19 % lower risk of death compared with the low-dose group, while men in the high-dose group instead had a 16 % higher risk[36]. Similar results with a positive impact on survival with higher Kt/V for women but not for men, was reported from a large registry study based on data from the DOPPS study and from a registry connected to Medicare in the US[38]. The question is whether women benefit more from higher dialysis doses. The V in Kt/V is a problem, not only for malnourished patients as described above but also for small patients and for women, who achieve a higher Kt/V with less dialysis. With a low V, a falsely high measurement of the dialysis dose is obtained. Thus, at the same measure of Kt/V, women receive less dialysis compared with men. A surface-area normalized formula, SAN-stdKt/V has been proposed as a way of decreasing this falsely high result. Ramirez et al has shown in observational data,

that survival continues to improve for both men and women in the highest percentiles of SAN-stdKt/V[39].

Impact of session length

The impact on survival of different session lengths for hemodialysis patients with dialysis thrice weekly has been analysed in large registry studies. The DOPPS study showed, that for European, Japanese and American patients, three weekly sessions with a duration longer than 240 min per session resulted in a 19 % lower (RR 0.81) relative risk of mortality compared with patients with a duration shorter than 240 min per session[29]. Other studies from the US, reported a 26 % (HR 1.26)[40] and a 42 % (HR 1.42)[41] increase in mortality for prevalent and incident patients, respectively, with sessions shorter than 240 minutes. Moreover, the DOPPS study reported that for sessions with a duration between 180 and 270 minutes, every 30 minutes increase in duration was associated with a 7 % lower relative risk (RR 0.93)[29]. Brunelli et al, reported that for every 15 minutes decrease in session duration from a standard of 240 minutes, there was a 12 % increase in mortality risk (HR 1.12)[41].

Impact of interdialytic interval

The frequency of dialysis sessions is another important factor. Large registry studies have reported a daily variation in deaths for patients with dialysis sessions thrice weekly. An analysis from the DOPPS study reported higher overall mortality on Mondays for patients with a Monday, Wednesday, Friday schedule and on Tuesdays for patients with a Tuesday, Thursday and Saturday schedule[42]. Foley et al, reported an increased mortality from all causes, cardiovascular diseases and infectious disease, the day after the two-day dialysis interval in a cohort of 32 000 dialysis patients from the US[43]. Krishnasamy reported a significantly higher frequency of cardiac deaths on Mondays and a trend towards a higher frequency on Tuesdays for patients in the ANZDATA registry with dialysis thrice weekly[44].

Dialysis twice weekly

Despite these results, indicating an increased risk with long dialysis intervals, a twice weekly dialysis schedule has been proposed for incident patients during recent years. Several possible advantages have been put forward, longer preservation of residual kidney function[45], less frequent cannulations of an immature vascular access and an easier transition for the patients to a life with dialysis[46]. However, the impact on survival has not yet been elucidated[46]. There is one study, based on data from the USRDS, reporting a lower mortality for prevalent patients treated twice compared with thrice weekly, and a borderline significant lower mortality for incident patients with twice compared with thrice

weekly dialysis sessions[47]. However, when residual renal function was included in the statistical adjustment for the subgroups of incident patients, the remaining difference in survival disappeared. No adjustment for residual renal function was performed for prevalent patients. In addition, for both twice- and thrice weekly dialysis schedules, the session lengths were only around three hours. Thus, two schedules with a very short total weekly dialysis duration were compared.

Observational studies on SDHD and NHD

In contrast, another growing trend is instead more intensive dialysis schedules, short-daily hemodialysis (SDHD) performed 5-6 times weekly or nocturnal hemodialysis (NHD) performed thrice weekly or more. These schedules have been compared with conventional hemodialysis (CHD), four hours, thrice weekly. Blagg et al compared survival for 117 patients with SDHD in-center or at home, with CHD patients included in the USRDS, using the and Standardized Mortality Ratio(SMR) Technique. In this analysis, the expected number of deaths for patients on SDHD was 25.7 and the actual deaths 10, during two years of follow up[48]. Kjellstrand et al extended this comparison and included 415 patients with SDHD performed both in-center and at home, from the US, France, U K and Italy[49]. He still found a significantly lower number of actual deaths 17 for patients with SDHD, compared with the expected 50.5 during two years of follow up. However, another small study by Johansen et al, could not confirm a significant advantage in survival for 43 patients on SDHD performed at home compared with propensity score matched patients with CHD, predominantly performed in-center[50]. There was a trend towards to a reduced risk with SDHD and, as the authors mention, the non-significance might be due to low power.

Survival for patients with long dialysis sessions, performed as nocturnal hemodialysis in-center, thrice weekly has been compared with survival for matched patients with CHD patients in two studies by Lacson et al[51] and by Ok et al[52]. The reported mortality risk for NHD patients compared with CHD patients was 25 % lower (HR 0.75) in the study by Lacson and 72 % lower (HR 0.28) in the study by Ok.

The most intensive dialysis schedule, NHD performed 5-7 times weekly has been compared retrospectively with CHD by Nesrallah et al[53]. Data about the patients on NHD were collected from the International Quotidian Dialysis Registry, comprising patients dialyzing at home from France, the US and Canada. The patients with CHD were recruited from the DOPPS study. The mean session duration for patients with NHD was 7.4 hours and the mean weekly frequency was 4.8. After a median follow up of 1.8 years the mortality risk with this intensive dialysis was reduced with 45 % (HR 0.55) compared with CHD. In another, smaller study by Johansen, comprising 94 patients with NHD, with a mean session duration of 7.5 and a mean weekly frequency of 5.7, the mortality risk was

reduced with 64 % (HR 0.36) in comparison with propensity score matched patients with CHD, predominantly performed in-center[50].

Although several observational studies have reported improved survival with more intensive dialysis, a study by Tennankore et al is the exception[54]. In this study, only patients with HHD were included. In comparisons between CHD (3-6 hours 2-4 times weekly) and NHD (6-8 hours 5 or more times weekly) or SDHD (2-3 hours 5 or more times weekly) no significant differences in survival was reported. Albeit, the explanation for these results might be low statistical power, due to low mortality for all three groups, as well as a high dialysis dose for some patients in the CHD group.

Randomized controlled studies on SDHD and NHD

Although the results of observational studies indicate a strong association between session length and weekly frequency and survival, there are no randomized controlled studies confirming these results. The Frequent Hemodialysis Network has compared two schedules performed in center, SDHD with CHD, and two schedules performed at home, NHD 6 times weekly with CHD, with two combined end-points; death or increase in left ventricular mass and death or change in self-reported physical health (RAND-36) after a follow up of 12 months. There were significant advantages for SDHD compared with CHD for both endpoints[55] but no significant differences between NHD and CHD for either of the endpoints[56]. In an extended follow up which compared survival between NHD and CHD, unexpectedly, a worse prognosis for NHD was found[57]. However, the authors, themselves, advice caution when interpreting the results, due to a high frequency of switches to other treatment modalities after the original study period of 12 months. There was also an unusually low mortality among patients with CHD, who probably were healthier than the average patient on CHD. In addition, the study was not powered for comparison of survival.

The combined impact of Kt/V and session length and frequency

According to large observational registry studies, Kt/V and the duration of dialysis sessions have a synergistic influence on survival for patients with dialysis sessions thrice weekly. The DOPPS study reported that for any treatment duration (analysed between 3 and 4.5 hours) an increase in Kt/V was beneficial, while the same was true for an increase in treatment duration with any level of Kt/V (analysed between 1.2 and 1.6)[29]. Similar results were reported in studies based on data from DAVITA dialysis clinics in the US[32] and from the ANZDATA registry[33]. However, in a study by Miller et al from the US, no beneficial impact on survival was reported with Kt/V above 1.8, especially for a subgroup of patients with treatment time above 4 hours. For this subgroup of patients, there was even a trend towards higher mortality with Kt/V above 1.8. In line with this,

Kjellstrand et al, reported no impact of Kt/V on survival for patients with more frequent dialysis, SDHD 5-7 times weekly[58]. Similar results have been reported in a study by Rivera et al, in an analysis restricted to patients with HHD[59]. No advantage was reported with higher Kt/V for this group of patients with a median frequency of 5 per week and a median treatment duration of 2.8 hours.

Even if several observational studies, as well as a secondary analysis in the HEMO study, have shown an improved survival with higher dialysis doses expressed as Kt/V, there seems to be a limit. Kt/V can only be used as a measure of the adequacy of the removal of small molecules in the blood compartment. However, with more intensive dialysis schedules, the clearance of phosphate and middle-sized molecules increases and the fluid balance improves, with a subsequent improvement in survival beyond which can be obtained exclusively by the clearance of small molecules, and measured as Kt/V.

Patient education

Several studies have shown that patient education plays an important role in the care of patients with chronic kidney disease. Patients who receive predialysis education, predominantly in CKD stages 4-5, feel that they are more able to participate in the choice of dialysis modality[60], are more willing to start self-care dialysis[61], and are less likely to start dialysis in a non-planned manner[62] or with a central venous catheter[61, 62]. They are also more likely to get a pre-emptive living-donor renal transplantation[63]. After starting dialysis, patients experience less anxiety, have less mobility problems and functional disabilities[64]. For patients starting hemodialysis, pre-dialysis education contributes to fewer and shorter hospitalizations at least during the first six months[65]. This is also related to lower total medical cost[65].

According to, two non-randomized and one randomized study, predialysis education does also improve survival[61, 66, 67]. However, there is probably some degree of selection bias in the observational studies. Wu et al compared the survival of patients with predialysis care in two centers in different geographical areas, one with and one without predialysis education[66]. Lacson et al compared survival for patients who choose the predialysis education after recommendation from their physician with patients who were not recommended the education or who chose not to participate[61]. However, in a randomized controlled study by Devins et al, a significant advantage in survival for patients with predialysis education persisted[67]. After a mean follow up of 8.5 years, this study reported 2.3 years longer survival for patients with predialysis education after the educational intervention and eight months longer survival after the their start of dialysis.

After start of dialysis, patient education might improve survival through increasing knowledge of some of the modifiable risk factors. Randomized studies in patients on hemodialysis have shown lower phosphate values[68], lower weight gains between dialysis sessions[69, 70] and improved compliance to taking medications up to 6 months after an educational program[71].

Modifiable risk factors inherent in CKD

There are several risk factors inherent in CKD, which affect patients' prognosis. Various hemodialysis prescriptions have been put forward to decrease these risks.

Fluid balance and blood pressure

For patients on dialysis, fluid overload, hypertension and left ventricular hypertrophy are tightly connected and important factors affecting the increased mortality[72-75].

Dekker et al reported a hazard ratio of mortality of 2.7 for patients with > 2.7 L pre-dialytic fluid overload compared with patients with normovolemia.[76] Wong et al reported, a hazard ratio of mortality of 1.23 for patients with an inter-dialytic weight gain above 5.7 % compared with patients with a weight gain of 2.5-4 %.[77]

High ultrafiltration rates, usually a consequence of high inter-dialytic weight gains, are also related to mortality[29]. Data from the DOPPS study show that the relative risk of mortality is 1.09 for ultrafiltration-rates above 10 ml/h/kg.

Contrary to the benefit, reported in the general population, of reduced blood pressure, several observational studies have shown a U-shaped association between blood pressure and mortality in patients on dialysis[78]. A predialytic systolic blood pressure < 110-120 mm Hg has been related to the highest risk of death[79, 80]. Results from the DOPPS study show that even a pre-dialytic systolic blood pressure of 120-129 was associated with a hazard ratio of 1.11 compared with 130-139[81]. However, Stidley et al analysed the association between blood pressure and survival for patients surviving more than 3 years on dialysis. For these patients, there only was an increased risk of mortality for those with a blood pressure above 150 mm Hg at baseline. Thus, the explanation behind the U-shaped relation between blood pressure and survival might at least to some extent be due to frailty in patients with low blood pressures and an overall increased risk[82].

Left ventricular hypertrophy, a consequence of fluid overload and hypertension, increases the risk of cardiovascular events, mortality and the risk of sudden cardiac death[83].

Pathophysiology

Hypertension for patients on dialysis is related both to the underlying renal failure and to fluid overload. An increase of 1 mmHg in pre-dialysis systolic blood pressure has been reported for every 1 % increase in inter-dialytic weight gain in relation to the target dry weight[84]. The high ultrafiltration-rates, that usually are the consequence of high inter-dialytic weight gains, increase the risk of intradialytic hypotension which in turn increases the risk of ischemia[85]. In addition, the hypertension and fluid overload increase the left ventricular mass with a subsequently increased risk of both chronic heart failure and ischemic heart disease[73].

Observational studies in patients on hemodialysis

Observational studies have reported that more intensive dialysis schedules have a positive impact on left ventricular hypertrophy and blood pressure compared with CHD. Improvement in left ventricular mass has been shown for both SDHD[86] and NHD[52, 87]. Studies with comparison between NHD and CHD reported lower blood pressure and less antihypertensive medicines for patients on NHD[52, 87].

Randomized controlled studies in patients on hemodialysis

In two randomized controlled studies, the systolic blood pressure has been reported to be 10-14 mmHg lower for patients on NHD compared to CHD after 6 or 12 months follow up, despite a greater reduction in antihypertensive medications for patients with NHD[56] [88]. Moreover, there was a significant improvement in left ventricular mass for patients on NHD compared with CHD in one of the studies [88] and a non-significant trend towards improvement in the other study[56]. In one of the studies, fewer hypotensive episodes for patients on NHD were reported.

Another randomized controlled study, which compared SDHD with CHD, reported a significant improvement in systolic blood pressure with 10 mmHg as well as in left ventricular mass for patients with SDHD[55].

Secondary hyperparathyroidism and the clearance of phosphate

Secondary hyperparathyroidism is closely related to both cardiovascular- and all-cause mortality in dialysis patients[89]. In addition to the increased cardiovascular

risk, secondary hyperparathyroidism is involved in bone remodelling disorders with either too high or too low bone turnover. Several studies have reported U-shaped relations between the laboratory values involved in the secondary hyperparathyroidism; phosphate, calcium and PTH (parathyroid hormone), and mortality[90-92]. Although some studies have found that high values[93] for all three parameters exhibit a stronger correlation with increased mortality than low values[91, 94].

Pathophysiology

The onset of secondary hyperparathyroidism happens already during CKD stage 3 with gradually rising phosphate levels due to impaired renal elimination[90]. The increased phosphate levels activate a compensatory mechanism, an inhibition of the phosphate re-uptake in the distal tubuli, mediated by fibroblast growth factor 23 (FGF 23) and its co-receptor alpha klotho[95]. However, FGF 23 and alpha klotho also inhibit the activation of vitamin D[95] and with a secondary decrease in calcium levels and increase in PTH levels[96]. Thus, in untreated secondary hyperparathyroidism, levels of phosphate and PTH are elevated while levels of calcium and vitamin D levels are low. Low PTH levels and high calcium levels might be a consequence of treatment with vitamin D analogues and calcium-containing phosphate binders.

Elevated levels of phosphate and calcium cause vascular calcifications mainly in the arterial media wall, which induces increased arterial stiffness and increased cardiovascular risk[90, 97]. FGF 23 has a stimulatory effect on the vascular calcification[98]. Increased PTH levels are related to myocardial fibrosis, through stimulation of fibroblasts and are involved in the progression of left ventricular hypertrophy[72].

Besides the renal clearance, the increased levels of phosphate, depends on nutritional intake, the amount of prescribed phosphate binders and the dialysis[90].

Observational studies in patients on hemodialysis

Observational studies have shown improved phosphate levels and fewer prescribed phosphate binders with more intensive dialysis schedules compared with CHD. Ayus et al reported lower phosphate levels and fewer prescribed phosphate binders in patients on SDHD compared with patients on CHD. Lockridge et al and Lacson et al, have reported a decline in the use of phosphate binders as well as a decrease in phosphate levels for patients starting NHD[51, 99]. In the study by Lockridge, 70 % of the patients required that phosphate was added to the dialysate despite nutritional advice from the dietitian aiming to increase the intake of phosphate [99].

Interventional studies in patients on hemodialysis

Increased dialysis doses, measured as Kt/V, does not necessarily correlate to an increased clearance of phosphate. In a study, which focused on interventions to increase Kt/V, there was no significant improvement in phosphate levels despite an increase in Kt/V from 0.9 to 1.2[100]. The higher Kt/V was achieved through increased blood and dialysate flow and only to a minor extent through increased dialysis duration, from 3.6 to 3.9 hours thrice weekly. Contrary to this, in a study, in which patients had one 4 hours and one 8 hours dialysis session, both with the same volumes of blood and dialysate processed, the phosphate concentration increased with 27 % in the dialysate after the longer session[101].

The reason for the weak correlation between Kt/V and the clearance of phosphate is the slow transfer of phosphate and the high rebound to the blood compartment after a dialysis session compared with a small molecule like urea. Even though phosphate has a low molecular weight, it is hydrophilic and surrounded by an aqueous cover, which increases its weight. In addition, it is mainly distributed intracellularly and has a slow transfer from the intra- to extracellular space[102].

Randomized controlled studies in patients on hemodialysis

Several randomized controlled studies have confirmed that a long-hours dialysis duration improves phosphate levels, even though none of the studies have shown an impact on the levels of PTH or calcium[56, 88, 103, 104]. Phosphate levels were 0.4-0.5 mmol/L lower with NHD compared with CHD, despite a reduction in the number of phosphate binders ordinated[88, 103]. The Frequent Hemodialysis Network has also compared SDHD with CHD and showed a less pronounced impact on the phosphate levels, of about 0.1-0.2 mmol/L with short frequent dialysis[55, 104].

Hemodiafiltration (HDF) has been proposed as another way of increasing the clearance of phosphate. However, most randomized controlled studies with comparison between HDF and HD with high and/or low flux filters have not shown any significant differences in phosphate levels[105-108]. Two studies randomized patients to either HDF or exclusively to HD with diffusive dialysis with a low-flux filter. No significant difference in phosphate levels was reported in the small study by Wizeman, which included only 44 patients[105]. However, in the larger Contrast study, which comprised 714 patients, there was a small but significantly lower phosphate level of 0.05 mmol/L[109] for patients on HDF.

In consequence, in order to decrease phosphate levels an increased weekly duration of dialysis seems to be the most efficient way.

Inflammation and malnutrition

Inflammation and malnutrition are associated with a worse prognosis for dialysis patients. Increased levels of inflammatory markers, such as albumin, CRP, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), are all related to increased mortality[110-112]. In addition, there is an association between clinical assessment of malnutrition using, Subjective Global Assessment (SGA) or anthropometric measurements and mortality[113].

Pathophysiology

Inflammation and malnutrition are not only independent prognostic factors but also tightly connected with each other and the risk of cardiovascular disease for patients with ESRD[110, 114]. The Malnutrition, Inflammation and Atherosclerosis Syndrome, MIAS, subgrouped into type 1 and type 2, is a model for explaining these associations. However for the individual dialysis patient, a mixed type is often present[110]. MIAS type 1 is caused by low nutritional intake because of factors associated with the uremia, and reversed by increased dialysis and nutritional support. In MIAS type 2 the nutritional intake might be normal but the resting energy expenditure is increased due to inflammation and comorbidities. The MIAS type 2 is not reversed by increased dialysis or nutritional support. In type 2, albumin is decreased, while this is not a typical attribute of type 1[110].

Observational studies in patients on hemodialysis

Theoretically, an improved prognosis with convective dialysis therapies, HDF or hemofiltration is plausible, as many inflammatory markers are middle-sized molecules and would be more easily removed with these therapies[114]. However, the DOPPS study did not reveal any differences in albumin levels for patients with either low- (<15 L infusion volume) or high- efficient (> 15 L) HDF compared with HD as exclusively diffusive therapy[115]. The observational RISCAVID study, did not find any significant differences in CRP for patients on HDF or HD as exclusively diffusive therapy. They did however, report significantly lower Il-6 for a subgroup of patients with high efficiency HDF with infusion volumes of 23 L per session compared with HD[112].

The impact on inflammatory markers of different dialysis doses, SDHD compared with CHD, was studied by Ayus et al[86]. In this observational study, patients on SDHD had lower CRP levels, 0.5 mg/L, compared with matched patients on CHD, 6.4 mg/L. However, there was no difference in the levels of albumin. Demirci et al reported higher albumin and lower CRP levels for prevalent patients on CHD who changed to in-center NHD compared with matched patients continuing with CHD[116].

There are few studies analysing the association between dialysis dose and nutrition. Albeit, an association between shorter dialysis session duration and patient reported lack of appetite was found with data from the DOPPS study[117]. There are three small observational studies, which focus on NHD and nutrition. Pierratos et al reported increased protein intake after start of NHD for incident and prevalent patients on dialysis, and a trend towards higher target weights[118]. Demirci et al reported increased fat mass and dry lean mass for prevalent dialysis patients who changed from CHD to NHD compared with matched patients continuing with CHD[116]. Finally, in a study by Ok et al, patients with NHD thrice weekly had higher body weight compared with matched patients on CHD[52].

Interventional studies in patients on hemodialysis

In another non-randomized prospective study by Azar et al, patients included in an intervention group with focused on increasing Kt/V, were compared with a non-intervention group[100]. The group focusing on increasing Kt/V, had higher albumin and normalized protein catabolic rate (nPCR) as indicators of decreased inflammation and improved nutrition.

Randomized controlled studies in patients on hemodialysis

In line with the observational studies, most randomized controlled studies have not found any significant differences in CRP or albumin between patients treated with HDF, hemofiltration or HD as exclusively diffusive therapy [105, 107, 108, 119]. The Turkish OL-HDF study is an exception reporting significantly higher albumin levels for patients with high-efficiency HDF, though with a very small difference in absolute numbers, 39.9 compared to 39.3 g/L [108]and no difference in CRP.

The NHD [56]and SDHD[55] studies performed by the Frequent Hemodialysis Network study group also compared albumin levels between NHD or SDHD and CHD. However, in these randomized controlled studies there were no significant differences in albumin levels.

Thus, so far, most studies show no impact of HDF or hemofiltration on inflammatory markers. Some observational studies show an association between more intensive dialysis schedules and inflammatory markers, while no difference was reported in randomized controlled studies by the Frequent Hemodialysis Network group. It is still not clear if the differences reported in observational studies are confounded by differences in patient selection.

Renal anemia

Severe anemia has been shown to increase mortality in patients on dialysis[111, 120] and has been shown to have an impact on the progression of left ventricular hypertrophy[72].

Pathophysiology

The causes behind renal anemia are multifactorial and mediated through decreased renal production of erythropoietin, insufficient levels of iron and a depressed erythropoiesis [121, 122]. The low plasma levels of iron are caused by increased blood loss due to blood tests, because of anticoagulation treatment during dialysis and due to subclinical bleeding from the gastrointestinal tract. Inflammation with increased hepcidin levels, which result in a decreased uptake of iron from the gastrointestinal tract and increased trapping of iron in macrophages and in hepatocytes also contribute [121, 123]. The depressed erythropoiesis is mainly due to decreased production of erythropoietin in the endstage kidney despite anemia. There are other contributory factors, such as iron deficiency, a negative impact on the bone marrow of inflammatory cytokines, increased PTH and uremic toxins[121, 122, 124]. In addition, insufficient levels of calcitriol can affect erythropoiesis, as it is related to fewer erythropoietin receptors and a lower responsiveness to erythropoietin[124].

Treatment with Erythropoiesis Stimulating Agents

Treatment with Erythropoiesis Stimulating Agents (ESA), at least to a target level of haemoglobin of 100-115 g/L, improves the survival[125-127]. However, higher target levels of hemoglobin have been associated with vascular access thrombosis, stroke and mortality[125, 126]. The mechanisms behind the negative impact of higher hemoglobin levels or higher ESA doses might be increased blood pressure, increased blood viscosity or increased number and activation of platelets related to the ESA-doses [125]. The necessity of high doses of ESA, which is usually due to ESA resistance which can be a consequence of inflammation, a dysregulated secondary hyperparathyroidism and uremic toxins[121] is an indirect prognostic marker related to higher mortality[122].

Observational studies in patients on hemodialysis

Results from several observational studies have shown that longer or more frequent dialysis sessions improve hemoglobin levels and decrease the ESA doses needed. The DOPPS study reported that patients with treatment durations of 180 min had on average a 9 g/L lower hemoglobin concentration compared with patients with longer dialysis sessions of 270-300 min[128]. Other small observational studies have shown higher hemoglobin levels for patients on NHD

compared with CHD. However, there was no pattern concerning ESA dose and dialysis duration in these studies[129-131].

Studies comparing SDHD and CHD have reported higher or stable hemoglobin levels over time for patients on SDHD despite lower ESA doses[86, 130]. Similar results have also been reported from cross-over studies, showing improved hemoglobin levels concomitant with reduced ESA doses in patients on CHD who switched to NHD[132] or SDHD[133].

Interventional studies in patients on hemodialysis

The impact of an increased dialysis dose, directly on the erythropoiesis, has been studied by Chan et al[134]. They found a superior growth of hematopoietic progenitor cells when cultured in plasma from patients treated with NHD compared with plasma from patients treated with CHD.

Randomized controlled studies in patients on hemodialysis

In contrast, in two randomized control studies, no significant benefit was reported with more frequent dialysis. Culleton et al randomized 51 patients to NHD 6 times weekly or CHD 3 times weekly and found no significant difference in hemoglobin concentration or the ratio of ESA dose to hemoglobin[88]. The Frequent Hemodialysis Network randomized 245 patients to SDHD or CHD and 87 patients to NHD[55] or CHD[56] and found no significant differences in ESA dose[55]. However, they did find a small significant difference in hemoglobin concentration, 119 g/L for SDHD and 117 g/L for CHD patients[135].

The impact of HDF on hemoglobin and prescribed ESA doses, has been compared with HD (exclusively performed as a diffusive treatment) with high- or low-flux filters in several randomized controlled studies[105-108]. There was only one study which reported a small but significant increase in hemoglobin in patients with HDF compared with exclusively low-flux HD: 118 and 116 g/L, respectively[109].

The impact of hemodialysis on renal anemia is still not fully elucidated. The divergent results between observational and randomized controlled studies focusing on dialysis dose might be related to patient selection. It is possible that patients with an overall superior prognosis and higher hemoglobin levels were allocated to more intensive dialysis schedules in observational studies. Should the removal of uremic toxins have a positive impact on erythropoiesis, more frequent dialysis might on the other hand cause a greater loss of hemoglobin.

Residual renal function

Preserved residual renal function (RRF) is associated with an improved survival for dialysis patients[136-138]. It affects several prognostic factors: fluid balance, bone mineral metabolism, anemia and clearance of middle molecules such as beta 2 microglobulin[136, 137].

Pathophysiology

Besides the etiology of the primary renal disease and certain comorbidities, factors related to hemodialysis per se affect the decline in RRF, such as inflammation due to exposure to the dialysate and dialyser membranes[136] or ischemia caused by hypotensive episodes or intravascular volume depletion[45, 136, 139].

Observational studies in patients on hemodialysis

Earlier studies have shown that RRF is better preserved with PD compared with hemodialysis[139, 140]. However, in a study comparing hemodialysis using newer synthetic high flux membranes and ultrapure dialysate, there was no difference in the decline of RRF for incident hemodialysis patients in comparison with incident PD patients[141]. McCarthy et al reported a lower monthly decline of RRF, 0.14 ml/min for patients using synthetic polysulfone dialyser membranes compared with cellulose acetate membranes, 0.27 ml/min[142].

In addition to type of membrane and dialysate, the frequency and duration of the hemodialysis sessions might have an impact on the preservation of RRF. There are two observational studies reporting a better preservation of the RRF with dialysis twice weekly compared with thrice weekly[45, 143].

Randomized controlled studies in patients on hemodialysis

Different dialyser membranes and dialysates have also been compared in randomized controlled studies. Hartman et al, reported a decline of 0.99 ml/min during three months with cellulose acetate membranes compared with 0.6 ml/min for synthetic polysulfone membranes[144]. Schifffl et al, compared ultrapure dialysate with commercial potentially microbiologically contaminated dialysate for patients on hemodialysis with high-flux membranes. A significantly slower decline in RRF was reported for patients with ultrapure dialysate. Both groups had a clearance of 7.9 ml/min at inclusion, while after 24 months of follow up the RRF was 4.3 ml/min for patients with ultrapure dialysate compared with 2.5 ml/min for patients with the commercial dialysate[145].

The Frequent Hemodialysis Network have compared the impact of different dialysis schedules on the residual renal function[146]. Patients randomized to CHD had a significantly slower decline in RRF compared with patients with frequent NHD (6 weekly). Albeit, there was no difference in the rate of decline of

RRF between patients randomized to SDHD compared with patients on CHD. The nonsignificant results in the comparison between SDHD and CHD might be caused by low power in this part of the study. Both groups of patients with SDHD and CHD had a low RRF (GFR around 2 ml/min) at baseline.

Thus, observational and randomized controlled studies indicate that synthetic polysulfone dialysis membranes and ultrapure dialysate are associated with a slower decline in RRF. In addition, some observational and randomized controlled studies indicate that more intensive dialysis schedules are associated with a more rapid decline in RRT. Possible explanatory factors behind this, might be a less expanded blood volume, intradialytic hypotension and increased inflammation with more frequent dialysis[45, 136, 146].

Metabolic acidosis

Metabolic acidosis has a negative impact on patients with CKD. It increases whole body and muscle protein catabolism, enhances bone mineral disorder, can accelerate the progression of CKD, impairs growth hormone and thyroid hormone secretion, decreases insulin sensitivity and increases accumulation of beta 2 microglobulin [147, 148].

Pathophysiology

In CKD, the production of acid, exceeds the ability of the kidneys to reabsorb filtered bicarbonate and excrete acid, thus causing metabolic acidosis. Dietary intake is the main factor influencing the production of acid, with animal proteins causing more acidosis than fruit and vegetables[148]. For patients in a catabolic state, breakdown of endogenous protein contributes to an increased acidosis [149].

Observational studies in patients on hemodialysis

The treatment of metabolic acidosis consists of oral sodium bicarbonate for non-dialysis dependent patients. For dialysis patients, buffers in the dialysate fluids correct the acidosis[147, 148]. However, the correction of the acidosis for patients on HD is not only related to the bicarbonate concentration in the dialysate but also to some extent, to the dialysis dose[149], the frequency and duration of the dialysis sessions as well as blood and dialysate flow rates[147].

There are no randomized controlled studies, that clarify the ideal target for predialysis serum bicarbonate or bicarbonate concentrations in the dialysate. Several observational studies have shown a higher mortality for patients with lower predialysis serum bicarbonate[111, 148]. However, data from the DOPPS study [150]and a large observational study by Wu et al, from a dialysis provider in the US[151], showed a U-shaped association with the best survival for patients

with serum bicarbonate between 17 and 27 mmol/L in the DOPPS study and 17 and 23 mmol/L in the study from the US. This association changed after adjustment for confounding factors in the study by Wu et al but not in the DOPPS study. When factors associated with a worse prognosis such as nutrition, comorbidity and inflammation were included in the cox model, the association between low values and mortality was even stronger, while the association between mortality and the high values became weaker. High predialysis serum bicarbonate is related to malnutrition, as diet is the main contributor to acid production, but also to inflammation and higher comorbidity[147, 148]. Thus, the association between high serum bicarbonate and higher mortality might not be causal.

Other observational studies have reported an association between high bicarbonate concentrations in the dialysate and mortality[147, 148, 152, 153]. This association might be causal through cardiac or infectious mechanisms. A high bicarbonate concentration in the dialysate might cause alkalosis, which increase the risk of hypocalcemia, hypokalemia, arrhythmias and increased vasodilation with subsequent ischemia[147]. In the DOPPS study, the increased mortality associated with high bicarbonate concentrations in the dialysate, was mainly related to an increased mortality in infectious diseases [153], which might be caused by a negative impact on the immune system by alkalosis[148, 153]. However, it is not unreasonable that the association between high dialysate concentrations of bicarbonate and increased mortality could be caused by confounding factors in patients who already have a worse prognosis and low serum bicarbonate concentration[152]. In the DOPPS study, there was no significant relation between survival and the concentrations of bicarbonate in the dialysate, when analysed for subgroups of patients with different levels of serum bicarbonate[153]. Thus, the ideal target for dialysate or serum bicarbonate is not known.

Accumulation of beta 2 microglobulin and middle-size molecules

Beta 2 microglobulin is used as a marker of the accumulation of middle-sized molecules and is also in itself related to increased mortality in dialysis patients[154-156]. It has clinical effects through amyloid deposits in the osteo-articular system, most frequently as carpal tunnel syndrome[155, 157].

Pathophysiology

Beta 2 microglobulin is a polypeptide included in the Human Leukocyte Antigen (HLA) class 1 molecule, with a molecular weight of 11.8 kDA. The levels of beta 2 microglobulin rise in patients with CKD due to impaired renal elimination and increased inflammation[154]. The increase in mortality is caused by amyloid

deposits in the the myocardium, endocardium, small vessel walls and epicardial veins, as found in autopsy studies[157].

Observational studies in patients on hemodialysis

As beta 2 microglobulin is a large molecule compared with urea, it has a slower transition between compartments within the body and over dialyser membranes. Three ways of increasing its clearance during hemodialysis have been proposed: high-flux filters, convective dialysis therapies such as HDF or hemofiltration, and more frequent or longer dialysis sessions. This is one of the few fields within nephrology in which randomized controlled studies are common, while there are few observational studies.

Crossover studies have shown increased clearance of beta 2 microglobulin with longer dialysis sessions, 6 or 8 hours, compared with 4 hours[101, 158, 159]. Albeit, in a study with focus on SDHD performed for 1.5-2 hours 6 times weekly compared with CHD, no significant difference in the predialysis values or clearance of beta 2 microglobulin was found[160]. Thus, the length but not the frequency of dialysis sessions seems to have an impact on the elimination of beta 2 microglobulin.

Randomized controlled studies in patients on hemodialysis

High-flux and low-flux dialysis membranes have been compared in two large randomized studies, the MPO (Membrane Permeability Outcome) and the HEMO (HEMOdialysis) studies. Both studies have reported lower levels of beta 2 microglobulin in patients treated with high flux compared with low flux membranes[161, 162] but neither study showed any effect on survival, which was the primary end-point. However, for subgroups of patients, those with albumin less than 40 g/l in the MPO study and for those with more than 3.7 years of dialysis vintage in the HEMO study, dialysis with high-flux filters was related to an improved survival[36, 162].

There are several randomized controlled studies, reporting improvement in beta 2 microglobulin levels with HDF or hemofiltration compared with hemodialysis (performed exclusively as a diffusive dialysis treatment), with high-flux or low-flux membranes[105, 106, 109, 119]. Some of these studies, but not all, report an advantage in survival with convective therapies [109, 119]. High-efficiency HDF, with a certain amount of substitution volume, seems to be required in order for the treatment to have an impact on survival. There is also one small study by Santoro et al reporting a borderline significant improvement in survival for hemofiltration compared with low-flux HD. Significantly improved survival was reported in the ESHOL study, with substitution volumes above 18 L[107], in subgroup analyses in the Turkish OL-HDF study for patients with substitution volumes above 17.4 L

[108] and in the Contrast study for patients with substitution volumes above 22 L [109].

Longer dialysis sessions, high-flux filters and HDF or hemofiltration have an impact on the levels of beta 2 microglobulin. The impact on survival differ between studies. High-flux filters might have an impact on the survival for subgroups of patients who have an overall worse prognosis. In addition, some studies show an impact on survival with high-efficiency HDF.

Survival with HHD compared with other RRT

Several previous studies, based on data from renal registries, have reported an improved survival for patients treated with HHD compared with patients with other dialysis modalities, even though the survival rates have been divergent. The five-years survival rates for populations of patients treated with HHD, is reported to have been 52 %-89 % between 1960 and 1990 [163-167]. In line with the overall improved prognosis for patients with dialysis, the five- year survival rates are higher, 79-88 %, in most studies reporting data after 1990[164, 168].

Patient selection must be taken into account, when comparing survival on HHD with other RRT. Age,[163, 169] the number of comorbidities[58, 168], and renal diagnosis[163, 169] have an impact on survival for patients on HHD while sex does not have an impact, according to most studies[58, 163, 166, 168]. Patient selection is controlled for with varying preciseness in different comparisons between HHD and the other RRT.

Survival with HHD or IHD

Most studies report a superior survival for patients with HHD compared with patients on IHD[1, 24, 58, 170-173]. The mortality risk for HHD compared with IHD was reduced with 13-42 % in studies from the the US[170, 171] and with 52 % in Australia and New Zealand[173]. A European study, from Switzerland, reported five- and ten- years survival which was 93 % and 72 % for HHD compared with 64 % and 36 % for IHD[1]. However, there are exceptions, in a study by McRae et al, there was no difference in survival between HHD and IHD[174] and in another study by Nitsch et al, there was a trend towards superior survival for HHD but no significant differences.

There are several possible explanations for the differences in the results between studies. How patients are allocated to different modalities differ between countries. Moreover, differences in patient selection between modalities is not

always treated with the same stringency. Comorbidity is one of the major differences between patients in the different treatment modalities. Most studies include separate comorbidities in statistical adjustments or in propensity score matching together with other variables, but only one of the older studies, by Saner et al used a validated comorbidity index, the Kahn index[1]. A study by McRae et al, is an example of the importance of considering patient selection[174]. In this study, separate comorbidities were included in statistical adjustments. No advantage was reported for patients on HHD, most probably because patients treated with assisted hemodialysis in nursing homes were defined as patients on HHD. Despite statistical adjustment, those patient's poor prognosis, had an impact on the results.

Differences in organization and praxis of the dialysis care and dialysis doses are other important factors. The reported relative advantage for HHD has been higher in Australia, New Zealand[172, 173], and in older studies from the US[170], compared to more recent studies from the US.[171] This is probably to some extent, a reflection of dialysis dose. HHD, in the more recent studies from the US, is exclusively performed with low dialysate flow dialysis devices, which requires longer or more frequent dialysis sessions for the delivery of an adequate dialysis dose. In other parts of the world, high dialysate-flow dialysis devices similar to those used for IHD, are more common.

In some studies, the focus has been on comparisons between HHD and IHD with different dialysis schedules. In a study from Australia and New Zealand, Marshall et al separated frequent or extended HHD and HHD performed as conventional HD, 4 hours thrice weekly[172]. Both types of HHD were associated with a similar and superior survival compared with IHD, with mortality risks reduced with 47 % and 49 % compared with conventional IHD, respectively. Kjellstrand et al included patients on dialysis in the US, between 1982 and 2005 and compared SDHD performed at home or in center and reported a 3.39 times higher mortality risk with SDHD performed in center[58]. In another study from the US by Johanson et al, comprising patients with dialysis during later decades, 1997-2006, no advantage was reported for SDHD at home (median 2.8 hours 5 times weekly) compared with IHD performed as conventional hemodialysis, 4 hours thrice weekly[50]. Whether this is related to less efficient dialysis with low dialysate flow devices is not clear. In the same study, a clear advantage was reported for HHD performed as nocturnal hemodialysis compared with IHD.

There are also several methodological differences between the studies. Some studies include prevalent patients, while others focus on incident patients, and some restrict the inclusion to patients surviving the first 30-90 days on dialysis. The follow up is according to intention to treat analysis in some studies, while others perform censoring at the dates of renal transplantation or at dates of any

change of RRT. The duration of the follow up according to intention to treat analysis is less than 10 years in most studies, but with a few exceptions such as the study by Saner et al, in which, the patients were followed for up to 30 years[1].

Even though most studies, report an advantage for HHD compared with IHD, the long-term outcome for incident patients starting on HHD compared with IHD is still not fully investigated, especially after matching for prognostic comorbidity indices and in the context of a European dialysis praxis.

Survival with HHD or PD

Most studies, comparing survival on HHD and PD, have shown an advantage for HHD. There is one small study with inclusion of patients from a few clinics in Scotland during the 1980s[175] as well as several larger studies based on data from renal registries comprising patients starting HHD or PD between 1997 and 2012: USRDS[176, 177], ANZDATA[24, 178] and UK renal registry[179]. Survival for patients on HHD was higher both for incident and prevalent patients and both when considering changes to other modalities, in per protocol analyses, and as intention to treat analyses.

Studies from Australia, New Zealand[178] and the UK[179] have reported reduced mortality risks of 39-66 % for HHD compared with PD, while the risk reduction for HHD was lower in studies from the US, 20-25 %[176, 177].

As described above when discussing data from the US for the comparisons between HHD and IHD, there are several possible explanations for the smaller advantage for HHD reported from the US. Patient selection is dealt with differently in studies focusing on HHD and PD. In most of the older studies, no matching or adjustment for comorbidities was performed. A validated comorbidity index has not been used in any of the previous studies. In the study by McRae[174] mentioned above, there was no advantage for HHD in comparison with PD, probably related to patient selection.

Dialysis dose might also have an impact on the results when comparing HHD and PD. One of the most recent studies from the US did not find an advantage for HHD in a sub-group analysis, which was restricted to incident patients on HHD or PD with less than 6 months of dialysis vintage[176]. Despite, dialysis 5-6 times weekly, the dialysis dose with the low-flow dialysate device does not seem provide an advantage compared with incident PD patients while most of the patients still have an additional clearance from their residual renal function.

Although most studies point to an advantage in survival for patients on HHD compared with PD, the relative impact of patient selection, especially differences in comorbidity, is still not fully elucidated. In addition, there is no study reporting

long-term follow up during decades, and for incident patients, the results are divergent between studies.

Tabel 1
Studies comparing survival between HHD and IHD or PD

Author	Setting	Patients (n) Incident/prevalent	Methods	Results	Follow up (years)
HHD and IHD					
Woods[170]	1986-1987 US	HHD 70 IHD 3102 Incident	Statistical adjustment (sex, age, diabetes, 25 separate comorbidities) Intention to treat:	HHD/IHD HR 0.58 (0.35-0.95)	4
Saner[1]	1970-1995 Switzerland	HHD 58 IHD 58 Prevalent	Matching sex, age, start date of RRT, renal diagnosis and statistical adjustment (Kahn Comorbidity Index, smoking, marital status) Intention to treat	5,10 20 years survival; HHD 93 %, 72 %, 34 %, IHD 64 %, 48 %, 23 %	30
Johansen[50]	1997-2006 US	HHD (as NHD) 94 HHD (as SDHD) 43 IHD (as CHD) 10 matching patients for each NHD and SDHD Prevalent	Matching propensity score (sex, age, separate comorbidities, dialysis vintage, renal diagnosis, BMI, diabetes nephropathy, hospital admissions) "on dialysis treatment only" ¹	NHD/IHD 0.36 (0.22-0.61) SDHD/IHD 0.64 (0.31-1.31) non significant	3
Kjellstrand[58]	1982-2005 US Europe	HHD (as SDHD) 189 IHD. (as SDHD) 73 Prevalent	Statistical adjustment (sex, age, renal diagnosis, dialysis vintage, start before 2000, dialysis prescriptions) Per protocol ²	IHD/HHD HR 3.39 (1.92-5.99)	18
Marshall[172]	1996-2007 Australia New Zealand	HHD (as frequent/extended) 865 HHD (as CHD) 2325 IHD (CHD) 21184 Incident	Statistical adjustment (sex, age, renal diagnosis, GFR at start, late referral, BMI, comorbidities, smoking, state, race, year of treatment) Per protocol ²	Frequent/extended HHD/CHD HR 0.53 (0.41-0.68) Conventional HHD /IHD HR 0.51 (0.44-0.59)	12
Weinhandl[171]	2005-2008 US	HHD (as SDHD) 1873 IHD (as CHD) 9365 Prevalent	Matching "as good as possible, according to pre-specified factors, with 5 matches" and statistical adjustment (age, admissions, EPOdose, BMI, transplant waitlisting, heart failure, ESRD duration, race, cancer, renal diagnosis, cerebrovascular disease, peripheral vascular disease, other cardiovascular disease, diabetes, atherosclerotic heart disease, sex, medicare/medicaid eligibility) Intention to treat	1, 2, 3 years HHD 89 %, 80 %, 73 %, IHD 87 %, 78 %, 79 % HHD/IHD HR 0.87 (0.78-0.97)	4
Marshall [173]	1997-2011 New Zealand	HHD 1547 IHD 8713 Incident	Statistical adjustment (sex, age, race, renal disease, GFR at start, late referral, diabetes, BMI, coronary heart disease, peripheral vascular disease, cerebrovascular disease, chronic lung disease, smoking, Hb, year of start) Per protocol ²	HHD/IHD HR 0.48 (0.32-0.53)	15

HHD and IHD or PD								
McRae[174] J	1995-2004 US	HHD 1641 IHD 419435 PD 37253 Incident	Statistical adjustment (sex, age, race, renal diagnosis, diabetes, history of CVD, functional status, era of dialysis start, household income, employment status) Intention to treat	HHD/IHD HR 1.1 (1.04-1.17) HHD/PD HR 1.04 (0.98-1.11) non significant	10			
Nitsch[179]	1997-2005 UK	HHD225 IHD 225 PD 225 Incident	Matching for sex and age and statistical adjustment (sex, age, renal diagnosis, year of start of dialysis) Intention to treat;	Unadjusted 1 year HHD 97 %, IHD 90 % , PD 95 % After adjustment: HHD/IHD 0.68 (0.44-1.03) p=0.071 non significant HHD/PD 0.61 (0.4-0.93)	8			
Kazra[24]	2003-2011 Australia New Zealand	HHD with AV fistula/AV graft 357 IHD with AV fistula/AV graft 5729 PD 6665 Incident	Statistical adjustment (sex, age, year of start, renal diagnosis, coronary artery disease, lung disease, diabetes, peripheral vascular disease, cerebrovascular disease, smoking, late referral, race, BMI) Per protocol ²	HHD>IHD with AVFistula/AVGraft HHD>IHD with CDK HHD>PD	6			
HHD and PD								
Grant[175]	1982-1988 Scotland	HHD 139 PD 139 Prevalent?	Matched for age and sex. (Only nondiabetic patients included.) Intention to treat	1 year survival HHD 100 %, PD 96 %, 3 years survival HHD 94 % PD 85 %	5			
Nadeau-Fredette[178]	2000-2012 Australia New Zealand	HHD 706 PD 10710 Incident (< 12 months)	Statistical adjustment (sex, age, renal diagnosis, lung disease, coronary disease, peripheral vascular disease, cerebrovascular disease, diabetes, race, late referral, GFR at start, smoking, BMI, era of RRT initiation, country) Intention to treat	Unadjusted 1.2.5 year HHD 98 %, 95 % , 85 %, PD 89 %, 76 %, 44 % HHD/PD HR 0.34 (0.26-0.45)	6			
Weinhandl[176]	2007-2010 US	HHD (daily) 4201 PD 4201 Prevalent Incident (< 6 months) subgroup analysis	Matching propensity score (sex, age race, renal diagnosis, ESRD vintage, Medicare enrollment, several separate comorbid conditions, BMI, hospital admissions, transplant wait-listing, albumin , GFR, hemoglobin, dialysis provider affiliation, ESA dose, iron dose, iv vitamin D dose) Intention to treat	HR 0.8 (0.73-0.87) 1.2.3 years HHD 88 %, 78 %, 70 % PD 85 %, 74 %, 64 % Incident Subgroup non significant	4			
Nesralah[177]	2004-2011 US	HHD (daily) 3142 PD 2688 Prevalent Incident (<12 months) subgroup analysis	Matching for ESRD vintage, year of start of RRT, age and propensity score (sex, age, race, smoking, alcohol, drugs, private coverage, ESRD start year, duration of ESRD, weight, prior transplant, cancer, hypertension, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, diabetes, albumin, hemoglobin) "on dialysis treatment only" ¹	HR 0.75 (0.68-0.82) Incident Subgroup HR 0.65 (0.54-0.78)	2			

Hazard ratios (HR) is for HHD related to the other modality if not indicated. ¹ Censoring at dates of renal transplantation and lost to follow up ²Censoring at dates of all changes of RRT and lost to follow up

Survival with HHD or a renal transplantation

Survival on HHD and with a renal transplant has been compared with divergent results between studies. The first studies included patients between 1964 and 1983. In two studies from the US, patient survival with a transplant from a living donor was reported as similar or better compared with HHD, while survival with a transplant from a deceased donor was reported as worse compared with HHD[180, 181]. In a third study, from Canada, survival on HHD was reported as worse also in comparison with patients with a renal transplant from a deceased donor[182].

There are also more recent studies, after the introduction of cyclosporine as immunosuppressive medication. Kjellstrand, compared survival for 415 patients starting SDHD, at home (64 % of the patients) or in-center, between 1983 and 2005, in the US, Italy, France and the UK, with the survival for patients with a deceased donor renal transplants registered in the USRDS. After matching for age, sex, race and primary diagnosis, no significant differences were found[49]. Pauly compared survival for 177 patients starting NHD at home in Canada between 1994 and 2006 with patients with renal transplants registered in the USRDS[183]. After both matching and statistical adjustment for several factors, no significant difference in survival was found between NHD and patients with a deceased donor renal transplant although the survival was superior for patients with a living donor renal transplant (HR 0.51, 95 % CI 0.28-0.91).

The objection raised against these studies, which did not show an advantage for transplantation with deceased donors compared with HHD, is that the patients with renal transplants were exclusively from the US, which has a worse prognosis for renal transplantation compared with some countries[184], while the patients with HHD had a broader recruitment base. Tennankore, on the other hand, compared HHD and all categories of renal transplantation for patients only from Canada[184]. However, this comparison was performed as a combination between patient and treatment survival. In this study, there was a survival advantage for renal transplantation after statistical adjustment for a variety of factors. Molnar et al compared survival for propensity-score matched patients solely from the US on HHD with patients with any category of renal transplants. For these patients, treated between 2007 and 2011, there was a four times higher mortality risk for patients with HHD (HR 4.06, 95 % CI 3.27-5.04)[185]. The worse prognosis for HHD, was even more pronounced in an analysis restricted to patients older than 65 years (HR 4.74, CI 95 % 3.25-6.91)[186].

The relative impact on survival of HHD and renal transplantation is still not elucidated due to the divergent results between studies. Differences in the dialysis health care and the health care for patients with renal transplants between countries might explain some of the differences between studies. Moreover, some

studies report different results in comparisons between HHD and patients with deceased donor transplants or patients with living donor transplants, while other studies do not separate between different donor types.

Impact of dialysis modalities on subsequent renal graft survival

Many of the patients who start dialysis in Sweden are also on the waiting list for renal transplantation. In the new millennium, around 400 patients have received a renal transplant annually. Only 50 of these patients, had renal transplantation as their first RRT[8]. As patients on HHD generally are younger and have fewer comorbidities compared with other dialysis patients, their frequency of renal transplantation is higher in comparison with the overall dialysis population. For all patients who are waiting for a renal transplantation, it is an important question whether their pre-transplant dialysis modality has an influence on the function or survival of their subsequent renal graft. Generally, patients receiving their first renal transplant have a good prognosis. Among patients in Sweden with their first renal transplant, 90 % of those with a deceased donor transplant and 93 % of those with a living donor transplant, live without dialysis after 5 years[8].

Two small studies from Canada report no significant difference in the decline of eGFR between patients with nocturnal HHD or CHD as pre-transplant modalities and with follow up of one year[187] and up to 9 years[188], respectively. Other studies, have instead compared PD and hemodialysis, performed predominantly as IHD, showing no difference in death-censored graft survival between the modalities[189-191]. Thus, renal graft function after HHD or IHD, as pre-transplant modalities, is only compared for a subgroup with nocturnal HHD and not as graft survival. No previous study has reported comparisons of graft survival between HHD and PD as pre-transplant modalities.

Health care utilization with HHD compared with IHD or PD

Hospital admissions have been used as a proxy for morbidity and total health care utilization when comparing dialysis modalities. For patients on dialysis, dialysis technique failure is an additional cause of health care utilization.

All-cause hospital admissions

A small Swiss study, with inclusion of patients between 1970 and 1995, reported significantly lower rate of hospital admissions for patients on HHD compared with IHD, with long-term overall follow up during several decades[1]. However, two more recent, large registry studies from the US, comparing HHD and IHD, including patients between 2004 and 2009 with a short follow up of less than 2 years, did not show any significant differences in the admission rates, neither with follow up according to per protocol nor in intention to treat analyses between[192, 193].

The frequency of hospital admissions for patients with HHD and PD have only been compared in the US and the results are divergent. Two large recent registry studies[176, 192] and one small study with inclusion of patients on dialysis between 1979 and 1981[194] have reported advantages for HHD compared to PD in the frequency of admissions with follow up according to per protocol and in intention to treat analyses. However, no significant difference was reported between the modalities in a small single-center study by Kumar et al[195] or in a sub-analysis restricted to incident patients in a large registry study by Weinhandl et al[176].

Hospital admissions with cardiovascular disease and infectious disease

Recent registry studies from the US with comparison between HHD and IHD, have reported a significantly lower frequency of hospital admissions with cardiovascular diagnoses for patients with HHD compared to IHD. However, the frequency of admissions with infectious diagnoses was higher for patients with HHD, both with follow up according to per protocol[192, 193] and intention to treat[193]. Weinhandl et al reported the same advantages and disadvantages for HHD when the duration, in addition to frequency, of admissions with cardiovascular disease and infectious diseases were compared. Further subanalyses in the study by Weinhandl et al, showed that the higher rate of admissions with infectious disease diagnoses was mainly caused by access-related infections[193].

Both Weinhandl et al and Suri et al have also reported advantages for HHD regarding the frequency of admissions with cardiovascular diagnoses and infectious diagnoses, respectively, compared with PD with follow up according to per protocol and intention to treat[176, 192]. However, in sub-analyses restricted to incident patients, no differences were reported between the modalities[176].

Table 2
Hospital admissions with HHD and IHD or PD

Author	Setting	Patients (n) Incident/prevalent	Methods	All cause admissions	Admissions with cardio-vascular diagnoses	Admissions with infectious disease diagnoses	Follow up (years)
HHD and IHD							
Saner[1]	1970-1995 Switzerland	HHD 58 IHD 58 Prevalent	Matching sex, age, start date of RRT, renal diagnosis and statistical adjustment (Kahn Comorbidity Index, smoking, marital status) Intention to treat	HHD<IHD	Non significant		30
Weinhandl[193]	2006-2009 US	HHD (daily) 3480 IHD 17400 Prevalent	Matching propensity score (sex, age, renal diagnoses, ESRD duration, medicare/medicaid enrollment, several comorbidities, BMI, catheter insertion, hospitalization, wait-listing. Dialysis providerESA dose, iron dose, iv Vitamin D dose) Intention to treat and per protocol	Intention to treat Non significant Per protocol Non significant	Intention to treat Non significant Per protocol Non significant	Intention to treat HR 1.35 (1.24-1.46) Per protocol HR 1.34 (1.23-1.46)	5

HHD and IHD or PD							
Surij[192]	2004-2009 US	HHD (daily, 1.5-4.5 h) 1116 compared with PD 2784 HHD (daily, 1.5-4.5 h) 1187 compared with CHD 3173 Prevalent	Matching Start date RRT, ESRD vintage, sex, race, BMI, congestive heart failure, cancer, cerebrovascular disease, and propensity score (sex, age, race, BMI, diabetes, several comorbidities, prior transplant, medical insurance coverage, albumin, hemoglobin) Per protocol ¹	HHD/IHD HR 0.92 (0.85-1.0) HHD/PD HR 0.73 (0.67-0.79)	HHD/IHD HR 0.68 (0.61-0.77) HHD/PD HR 0.66 (0.58-0.74)	HHD/IHD HR 1.15 (1.04-1.29) HHD/PD HR 0.81 (0.73-0.90)	< 2
HHD and PD							
Rubin[194]	1979-1981 US	HHD 37 PD 56 Incident	Subgroup 16 patients matched (sex, age, race, income, education) Per protocol and intention to treat	HHD<PD	-	HHD<PD	2
Kumar[195]	2003-2007 US	HHD (daily) 22 PD 64	Statistical adjustment (sex, age, race, diabetes, dialysis vintage) Per protocol ¹	Admission rate non significant Length of stay HHD 3.3, PD 5.6 sign	-	-	< 2
Weinhandl[176]	2007-2010 US	HHD (daily) 4201 PD 4201 Prevalent Incident (< 6 months) subgroup analysis	Matching propensity score (sex, age, race, renal diagnosis, ESRD vintage, Medicare enrollment, several separate comorbid conditions, BMI, hospital admissions, wait-listing, albumin, GFR, hemoglobin, dialysis provider affiliation, ESA dose, iron dose, iv vitamin D dose) Intention to treat and per protocol ¹	Intention to treat: Admission rate prevalent HR 0.92 (0.89-0.95) Incident non significant Per protocol Admission rate prevalent HR 0.86 (0.83-0.89) Incident non significant	Intention to treat: Admission rate prevalent HR 0.85 (0.80-0.91) Incident non significant Per protocol Admission rate Prevalent HR 0.85 (0.79-9.92) Incident non significant	Intention to treat: Admission rate prevalent 0.89 (0.84-0.94) Incident non significant Per protocol Admission rate prevalent HR 0.82 (0.77-0.87) Incident non significant	4

Hazard ratios (HR) is for HHD related to the other modality if not indicated. ¹Censoring at dates of all changes of RRT and lost to follow up

Dialysis technique survival with HHD or PD

Failure of dialysis technique is the most common cause for patients with HHD or PD to change to another dialysis modality. The technique failure might be caused by an inability to manage self-dialysis or an absolute or relative medical contraindication for the specific dialysis modality. On the other hand, changes from IHD are rarely caused by failure of the dialysis technique, but rather with the intent of giving a patient individualized care with home dialysis or because of a transition to palliative care without dialysis.

An improved dialysis technique survival for HHD compared with PD, has been reported in several studies performed in different settings, including patients from the 1960's until 2012 as well as from different continents, Australia[178], Europe[175] and North America [176, 194]. The technique survival has been analysed separately from patient survival in most studies, with censoring at dates of death and dates of renal transplantation [175, 176, 178]. The two most recent studies reported reduced risks of dialysis technique failure for HHD compared with PD of 66 % from Australia and New Zealand[178] and 30 % from the US[176]. The reported dialysis technique survival at two years has been 73 % to 96 % for HHD[176, 196-198] compared with 63 % to 74 % for PD [176, 199, 200]in different studies. The divergent results between studies may have several reasons. Firstly, the definitions of technique survival differ between studies. In some studies, a shorter period than 60 or 90 days with a subsequent dialysis modality is not defined as dialysis technique failure, while the definition of technique failure in other studies is independent of the duration of the period with a subsequent modality. Secondly, in a study from Canada, with the highest reported technique survival, patients with assisted HHD were included, enabling a longer technique survival[196]. Thirdly, both patient selection and dialysis prescriptions can contribute to differences between studies. Nocturnal HHD is a factor related to prolonged technique survival[54, 201]. Finally, old age is a risk factor for worse technique failure for HHD[178, 196] as well as for PD [200] although for PD residual renal function[200] and fluid removal[199] are more important factors.

Aims

- To investigate the survival in Swedish patients on HHD as initial renal replacement therapy (studies I and III)
- To study the major non-modifiable factors predicting survival (study I)
- To study whether a survival benefit persists in patients treated with HHD compared with IHD and PD when controlling for major non-modifiable factors (studies II and III)
- To study the effect of HHD, as initial dialysis modality, compared with IHD and PD, on graft survival after subsequent renal transplantation (study III)
- To study the effect of HHD on morbidity, using health care utilization as a surrogate measure, compared with IHD and PD (study IV)
- To study the effect of HHD compared with IHD on some modifiable factors associated with survival (study II)

Method

Studies at a glance

Study	Design	Cohorts	Outcome
I	Retrospective observational single-center study	HHD	Survival Non-modifiable factors predicting survival
II	Retrospective observational matched pair-cohort study from two centers	HHD IHD	Survival Effect of modifiable factors associated with survival
III	Retrospective observational registry-based matched cohort study	HHD IHD PD	Survival Subsequent renal graft survival
IV	Retrospective observational registry-based matched cohort study	HHD IHD PD	Health care utilization

Patient populations

Definitions of initial renal replacement therapy

Patients with HHD, IHD or PD, as initial RRT, were eligible for the studies in this thesis. In studies I and II, HHD and IHD was defined as initial RRT if the start of training for HHD or the start of IHD was within 6 months of any RRT. In studies III and IV, HHD, IHD or PD as initial RRT was defined as the modality registered in the SRR at day 90 after start of RRT. A failing renal transplant or a period of recovered renal function before day 90 were exclusion criteria. To be defined as HHD, a patient was not allowed to have received PD before day 90. To be defined as PD, a patient was not allowed to have been treated with HHD before day 90. To be defined as IHD, no other RRT was allowed during the first year after start of RRT, except for transplantation after day 90.

Inclusion criteria

In study I, all patients starting HHD training at the Department of Nephrology, Lund University hospital between 1971 and 1999 were eligible for inclusion. The HHD patients were recruited to Lund University Hospital from all over the Southern Health Care Region.

In study II, patients starting HHD at Lund University Hospital 1983 between 2002, were eligible for inclusion if an appropriate IHD patient fulfilling the matching criteria listed below could be found among patients starting IHD at Malmö General Hospital. Patients on IHD from Malmö were chosen as an appropriate group for comparison as the referral of patients from Malmö to the HHD programme in Lund was low during the study period. In study II, only patients completing HHD training were included in the study, consequently only patients who had been on IHD for at least 72 days, the median training period for HHD, were accepted as matching controls.

The same cohorts of patients were included in studies III and IV. For these studies, all patients 18 years or older, registered in the SRR and starting RRT between 1991 and 2012 were eligible for inclusion. All Swedish patients starting HHD as initial RRT, during the study period, could be matched with patients starting IHD and PD and included in the study.

Matching

Patients treated with HHD as initial RRT were matched with patients starting with IHD in studies II, III and IV and patients starting with PD in studies III and IV. Matching was performed at day 0 of RRT, according to sex, age, comorbidity and date of start of RRT. In study II, matching age and start date of dialysis were defined as less than 5 years difference. In studies III and IV, a narrower definition of less than 3 years was used due to the larger patient populations.

Comorbidity indices

Comorbidity was defined according to Davies comorbidity index in studies I and II and according to Charlson comorbidity index in studies III and IV. Davies index was developed for patients with ESRD[202], while Charlson index was developed for all kinds of patients[203]. Their prognostic value for patients with ESRD, is equal between them when used together with age[204].

Davies comorbidity index is based on seven groups of comorbidities; malignancy, ischemic heart disease, peripheral vascular disease, left ventricular dysfunction, diabetes mellitus, systemic collagen vascular disease and other significant

pathology with impact on survival in the general population. Patients with none of these comorbidities have grade 0, those with 1-2 have grade 1 and those with 3 or more comorbidities have grade 2. The definition of each comorbidity according to Davies index includes more details than ICD codes and is difficult to use for registry data.

Charlson Comorbidity Index is based on 19 diagnoses, that are assigned a weight of 1-6 based on severity (Table 3). The sum total of the weights equals a score which is subsequently translated to the comorbidity index; score 0 to index 0, score 1-2 to index 1, score 3-4 to index 2 and score 5 or above to index 3. This index is possible to apply to registry data using ICD 9 and 10 codes for diagnoses according to algorithms developed by Quan et al[205]. Ivarsson et al translated diagnoses coded according to the ICD 7 and ICD 8 codes to the ICD 10 codes in the algorithm by Quan by using conversion tables from the Swedish National Board of Health and Welfare[206].

Table 3
Charlson Comorbidity Index

Assigned weights	Diseases
1	Myocardial infarct Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Connective tissue disease Ulcer disease Mild liver disease Diabetes
2	Hemiplegia Moderate or severe renal disease Diabetes with end organ damage Any tumor Leukemia Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor AIDS

Data collection

Patient characteristics at start of RRT and dates of start and changes between RRT were collected from patient records in studies I and II and from the SRR in studies III and IV. Comorbidities and discharge diagnoses and dates of hospital admissions were collected from the Swedish Inpatient Registry in studies III and

IV. Dates of death were collected from the Swedish Mortality Database in all studies.

In study I, data on dialysis prescriptions was recorded at start of HHD and at 12 months after start of HHD.

In study II, data on dialysis accesses were registered at start of HHD or IHD and at 18 months and prescriptions of dialysis and medications at 6 and 18 months after start of HHD or IHD. For HHD patients, blood pressure at the visit to the clinic in closest proximity to 6 and 18 months after start of HHD was recorded. For IHD patients, mean pre-dialysis blood pressure during the 6th and 18th month after start of IHD was recorded. All laboratory analyses during the period 6-18 months after start of HHD or IHD were collected from patient records.

For patients stopping HHD or IHD, before 12 months in study I and before 18 months in study II (because of transplantation, death or change to another dialysis modality), only data up to the date of such an event was used in the analyses.

Prescriptions of anti-hypertensive drugs and diuretics were recorded as Defined Daily Doses (DDD), according to WHO[207] and as number of drugs according to ATC-codes, according to WHO[208]. The number of prescribed phosphate binders was recorded according to ATC codes. Prescriptions of erythropoiesis stimulating agents (ESA) were recorded as DDD.

Swedish Renal Registry and Swedish National Inpatient Registry

The Swedish Renal Registry (SRR) was created in 2007 after a fusion of four preceding registries. SRAU (Svenskt Register för Aktiv Uremivård) was established in 1991 as a registry comprising all Swedish patients with RRT. SDDB (Svensk Dialysdatabas) was a registry founded in 2002, based on annual cross sectional studies in all Swedish patients on dialysis focusing on dialysis quality. Two separate registries, both in patients with non-dialysis dependent chronic kidney disease, were included in SRR and established as a CKD registry for the whole country. After 2007, DIAD (Dialysaccessdatabas), a registry of dialysis accesses was merged into SRR. Three new sections of the SRR have been created; a registry of renal biopsies, a registry of renal transplantations and a registry of Patient Related Outcome Measures (PROM), RAND 36.

The coverage and completeness are different in different sections of the registry, mainly related to when it was established. The RRT section of the SRR, which was used in studies III and IV in this thesis, has a coverage and completeness of

nearly 100 %[209]. All dialysis and transplant units report to the registry and the registered patients are regularly updated through contact persons at each unit.

Data from the SRR are regularly transmitted to the European renal registry, ERA-EDTA and to the USRDS registry in the US, and included in international comparisons.

The Swedish National Inpatient Registry is connected to the Swedish National Board of Health and Welfare. All counties are obliged to report all discharges, with dates of the hospital stay and diagnoses of the hospital admissions. The registry was created in 1964. Since 1987 the coverage is almost complete in all counties. The completeness is now more than 99 % and the diagnoses are valid with a positive predictive value of 85-95 %[210]. Since 2001, there is also a separate section of the registry for outpatient visits, even though the completeness is, to date, not as good as for the inpatient part[211].

Statistical analysis

Statistical analyses were performed using IBM SPSS statistics versions 19, 20 and 23. In studies III and IV, calculations of Charlson Index were performed using STATA software version 12 and definitions of groups and matching were made using SAS.

Survival with HHD and compared with IHD and PD

The day for start of HHD training was used as day zero in the survival analyses in study I. In studies II and III the day of start of RRT was instead used as day zero.

Survival analyses were performed with Kaplan-Meier estimates in all studies. Follow up was defined according to three approaches. The major survival analyses were performed as intention to treat, in which patients were considered at risk also after switches to other RRT and with censoring only at the end of the study. Analyses were also performed with follow up according to “on dialysis treatment”, with an additional censoring at the dates of renal transplantation. In study III, analyses according to “on initial RRT only” were performed, with additional censoring at any changes from the initial modality.

For comparisons between groups, log rank test was used in studies I and III, while Breslow test was used in study II.

As the patients were not matched according to primary renal diagnosis, this was included in a bivariable cox regression analysis, with follow up according to intention to treat, in the comparison of HHD with IHD and PD in study III.

Patient characteristics and survival

In study I, the impact of patient characteristics on survival was analysed with Kaplan Meier estimates and log rank test. Comparisons were performed between groups of patients with different sex, age, Davies comorbidity index, decade of start and primary renal diagnosis. In addition, multivariable cox regression analysis was performed to elucidate if age, comorbidity and year of start were independently related to survival.

Influence of subsequent renal transplantation on survival

In study I, an intention to treat analysis and an “on dialysis treatment only” analysis, were compared within the same patient cohort with HHD. Thus, survival for the cohort of patients with HHD, with impact and without impact of subsequent renal transplantations, were compared.

Subsequent renal graft survival

In study III, renal graft survival was compared for patients with a subsequent renal transplantation after their initial RRT. As the subgroups with subsequent transplants were not matched, multivariable cox regression analysis was performed including decade of start of RRT, sex, age and Charlson Index at day 0 for RRT, renal diagnosis, dialysis vintage at the date of transplantation and whether the graft was from a living or deceased donor. Graft failure was defined as the only event in this analysis. Censoring was performed at dates of death and at end of study.

Hospital admissions

In study IV, all-cause hospital admissions were compared in three ways, as annual admission rate, days admitted per year and time to first admission. Admissions with cardiovascular diagnoses or infectious disease diagnoses as principal or secondary diagnoses were compared as annual admission rate and time to first admission.

Only admissions from day 90 after start of RRT were included in the analyses. The follow up was defined in two ways: as “on initial RRT” until changes to other

RRT, and according to intention to treat. Censoring was performed at dates of death in both analyses of time to first admission.

Mann-Whitney test was used for comparisons of annual admission rates and days admitted per year. Time to first admission was compared with Kaplan Meier estimate and Breslow test.

Dialysis technique survival

In study IV, dialysis technique survival for HHD and PD was compared after day 90 with Kaplan Meier estimate and log rank test. Technique failure was defined as a change to another dialysis modality. Censoring was performed at dates of renal transplantation, recovered native renal function, death and at the end of the study.

Modifiable risk factors related to survival

Modifiable risk factors in HHD and IHD were compared in study II. Only matched pairs with complete values were included in each comparison and paired statistical tests were used.

Mc Nemar test was used for dialysis accesses and Wilcoxon matched-pairs signed rank test was used for dialysis prescriptions and medications.

Time-averaged values of the levels of phosphate, calcium, albumin and hemoglobin in plasma/serum were calculated using all analyses performed during the period 6-18 months after start of HHD or IHD. The calculations used an “area under the curve” approach and the number of data points varied between 1 and 60. Paired t-test was used for laboratory analyses.

Results and specific discussion

Patient characteristics

Patient characteristics for all cohorts in this thesis are given in table 4.

Sex

The majority of the patients in all study cohorts were male, 73-83 %. This preponderance is more pronounced than in the entire group of patients with RRT registered in the SRR comprising 59 % in 1991[212] and 64 % in 2016[8].

Age

In study I, the median age was 46 years, for all patients starting HHD as initial RRT during the period of 1971-1999. For all patients starting HHD as initial RRT in Sweden from 1991-2012 (studies III and IV) the median age was 50.1 years. In the beginning of the 1970s the mean age for all Swedish patients starting dialysis was 31 years[7] but in later decades it increased to older than 60 years[8].

Comorbidity

The majority of patients in all three studies had no comorbidities according to Davies comorbidity index in studies I and II and according to Charlson comorbidity index in studies III and IV. In contrast, 60 % of all patients starting RRT in Sweden, have at least one of the comorbidities registered in SRR (malignancy, diabetes, ischemic heart disease, hypertension, cerebrovascular disease, peripheral vascular disease)[15].

Primary renal disease

The cohorts were not matched according to primary renal disease. Glomerulonephritis was the most common diagnosis in all cohorts, followed by adult polycystic kidney disease except for the IHD and PD cohorts in studies III and IV, where diabetic nephropathy was the second most common diagnosis.

In study I, only one patient had diabetic nephropathy, which probably is a reflection of differences between decades in the allocation of patients to different dialysis modalities. Among all patients starting RRT in Sweden, diabetic

nephropathy has been the most common renal diagnosis since 1993, followed by glomerulonephritis.

The characteristics of the HHD cohorts differ in sex, age, comorbidity and renal diagnosis compared with patients starting RRT in Sweden. This must be taken into consideration when comparing outcomes between the different RRT modalities. For this reason the cohorts used for comparison in this thesis are matched for sex, age and comorbidity. Differences in renal diagnoses are considered and adjusted for statistically.

Table 4

Patient characteristics

	Study I	Study II		Studies III, IV		
Start of HHD as initial RRT	1971-1999	1983-2002		1991-2012		
	HHD	HHD	IHD	HHD	IHD	PD
Patients (n)	128	41	41	152	608	456
Sex, male (percent)	73 %	76 %	76 %	82 %	82 %	82 %
Median age (years)	46	51.5	53.9	50.2	50.1	50.1
Davies comorbidity grade:						
0	80 %	71 %	71 %	-	-	-
1	19 %	29 %	29 %	-	-	-
2	1 %	0%	0%	-	-	-
Charlson comorbidity index:						
0	-	-	-	63 %	63 %	63 %
1	-	-	-	28 %	28 %	28 %
2	-	-	-	8 %	8 %	8 %
3	-	-	-	2 %	2 %	2 %
Renal diagnosis:						
Glomerulonephritis	42 %	56 %	44 %	30 %	25 %	28 %
APCKD ¹	26%	27 %	22 %	15 %	10 %	9 %
Hypertension/Nephrosclerosis	7 %	2.4 %	5 %	6 %	7 %	5 %
Diabetes	< 1% (n=1)	2.4 %	12%	10 %	20 %	27 %
Other	23%	12 %	12 %	28 %	23 %	20 %
Unknown	0 %	0 %	5 %	6 %	12 %	9 %

¹ Adult Polycystic Kidney Disease

Renal replacement therapies

Median follow up and duration of RRT in studies I-IV are presented in table 5.

The majority of the patients in all cohorts had their first dialysis with their initial RRT according to the definitions in the studies, but 11-45 % had a short period with another preceding modality.

Most patients changed renal replacement therapy during the follow up and some had more than one period with their initial RRT. The duration of the initial period with HHD was 1.8-3.1 years.

Most patients in all cohorts and studies had a subsequent renal transplantation but it was most common among patients with HHD.

Table 5
Periods with different renal replacement therapies during follow up

	Study I	Study II		Studies III, IV		
	HHD	HHD	IHD	HHD	IHD	PD
Initial RRT						
Median duration (IQR) years						
First period with HHD/IHD/PD	3.1 (1.6-6.4; n=128)	1.8 (1.2-3.5; n=41)	1.7 (0.6-4.7; n=41)	2.1 (1.1-3.1; n=152)	2.3 (1.1-3.9; n=608)	1.4 (0.8-2.4; n=456)
Total treatment with HHD/IHD/PD	3.6 (1.88-7.4; n=128)	2.7 (1.4-6.7; n=41)	2.5 (1.0-8.6; n=41)	2.4 (1.2-3.6; n=152)	2.6 (1.3-4.9; n=608)	1.5 (0.9-2.7; n=456)
Other RRT Median duration (IQR) years						
Renal transplantation	N.A. ¹ (n=87)	10.6 (7.0-14.3; n=33)	11.7 (2.9-16.3; n=23)	8.9 (5.1-13.5; n=114)	8.6 (3.8-12.3; n=312)	8.4 (4.3-13.1; n=311)
HHD	-	-	0 (n=0)	-	3.2 (2.3-6.8; n=10)	0.8 (0.3-0.8; n=5)
IHD	N.A. ¹	1.4 (0.6-3.7; n=17)	-	2.3 (0.6-4.8; n=36)	-	3.0 (0.7-8.8; n=174)
PD	N.A. ¹	1.8 (0.04-1.8;n=2)	2.0 (1.2-3.2; n=4)	0	1.7 (0.6-2.7; n=15)	-
Total follow up Median duration (IQR) years						
All RRT	13.9 (7.8-21)	14.2 (10.0-18.2)	10.8 (3.7-16.5)	10.4 (5.9-15.4)	7.0 (2.8-12.8)	7.5 (3.4-13.8)

¹ Not available

Survival on HHD

Survival in patients on HHD as initial RRT, was analysed for two patient populations. All patients starting HHD in Lund between 1971 and 1998 were included in study I, a retrospective, observational, single-center study. All Swedish patients starting HHD between 1991 and 2012 were included in study III, a retrospective observational registry-study.

The five- and ten-year survival was 84 % and 68 %, respectively, for patients who started HHD, in the intention to treat analysis in study I. In contrast, the ten-year survival for all incident patients registered in the SRR and starting RRT (including renal transplantation) was 34 % during the same period.

The annual mortality rate during the first 20 years in study I was 4.9 %. In comparison, the annual mortality rate was 30 % as reported by SRR between 1991 and 1998.

In study I, the survival improved significantly for patients who started HHD in each later decade ($p = 0.003$). This is a reflection of the overall improved survival for patients with dialysis as reported in the SRR[8] as well as in renal registries from other countries[10, 13]. In line with the overall improved prognosis, the five- and ten-year survival was superior for all Swedish patients with start of HHD between 1991 and 2012 in study III, 91 % and 76 %, respectively.

Non-modifiable factors predicting survival

Patient characteristics

In study I, age, comorbidity and year of start of HHD were all independently related to survival using a multiple regression analysis ($p < 0.001$). For the age group < 30 years, 10-year survival was 87% compared with 38% for the age group > 60 years. For the 103 patients with Davies comorbidity index grade 0, 10-year survival was 74%. In contrast, the patients with grade 1 exhibited a 10-year survival of 46%. Sex and primary renal disease were not related to survival, although only one patient had diabetic nephropathy.

Primary renal diagnoses were not included in the matching. In the comparison between HHD and IHD in study II, no statistical adjustment for renal diagnosis was performed as diabetes nephropathy was included in Davies comorbidity index. In study III, despite the inclusion of diabetes mellitus in Charlson comorbidity index, primary renal diagnoses were included in the bivariable cox regression analyses together with the dialysis modalities (HHD, IHD and PD). These analyses showed an advantage in survival for HHD compared with IHD and PD, as

described in more detail below. Moreover, diabetic nephropathy was related to a worse prognosis in both comparisons (HHD versus IHD: HR 1.9 95 %, CI 1.3-2.8, $p=0.001$; HHD versus PD: HR=2.6 95 %, CI 1.5-4.3, $p<0.000$). In the comparison between HHD and IHD, adult polycystic kidney disease (HR 0.4 95 %, CI 0.2-0.6, $p<0.001$) and glomerulonephritis (HR 0.5 95 %, CI 0.4-0.8, $p=0.001$) were both related to an improved prognosis.

Influence of subsequent renal transplantation on survival

Although the majority of patients in all cohorts in this thesis had a subsequent renal transplantation, it was most common in patients starting HHD. To assess the contribution of renal transplantation to the superior survival for patients on HHD, we compared Kaplan Meier estimates as intention to treat with estimates as “on dialysis treatment” within the cohort on HHD in study I. This “on dialysis treatment” analysis, without the impact of subsequent renal transplantation, yielded a significantly shorter survival compared with the survival in the intention to treat analysis. The difference between these two curves was, however, not only influenced by renal transplantation per se. Patients who received a renal transplant were younger and had less comorbidities compared with patients who did not. To limit this effect, separate survival analyses were performed for patients with Davies Index grade 0 and age below 60 (Figure 4). When limiting the analysis to these patients starting HHD with a favourable prognosis, the significant difference between the intention to treat and “on dialysis treatment” survival curves disappeared ($p = 0.09$). For these patients, with HHD as initial RRT, subsequent renal transplantation did not yield a survival benefit.

Specific discussion

These results from study I, show the importance of adequate matching or, if that is not possible, adjustment for differences in patient selection when comparing different dialysis modalities.

Even though we did not find a significant impact of subsequent renal transplantation on survival in younger and healthier patients, this study was not aimed or designed to compare survival between HHD and renal transplantation. Renal registries report a pronounced benefit in survival for patients with renal transplants compared with patients on dialysis [8]. However, earlier studies have shown divergent results when comparing survival in HHD and renal transplantation [180-186].

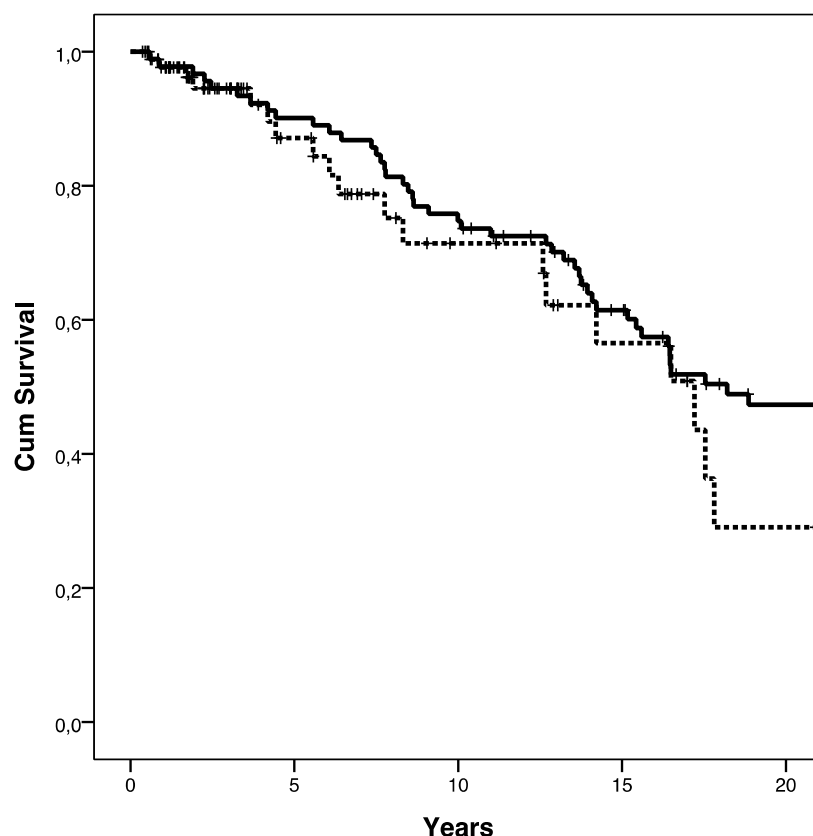


Figure 4

Long term survival with HHD and relative contribution of transplantation on survival with HHD, for a subgroup of patients with a good prognosis (younger than 60 years and Davies Index grade 0) starting HHD as initial RRT at Lund University Hospital during 1971-1998 (study I). The solid line in the Kaplan-Meier plot represents survival analyzed according to intention to treat. The dotted lines represent "on dialysis treatment" for the same patients. In the "on dialysis treatment" analysis censoring is performed at dates of renal transplantation. Comparison of the two Kaplan-Meier estimates shows that subsequent renal transplantation does not have an effect on survival for patients younger than 60 years and with no comorbidities ($p=0.09$)

Survival with HHD compared with IHD and PD

Comparisons according to intention to treat and "on initial RRT only"

Survival in patients treated with HHD or IHD as initial RRT was compared in study II, a retrospective observational study, comprising HHD patients from Lund University Hospital and IHD patients from Malmö General Hospital, and in study III, a retrospective registry study, comprising all Swedish patients treated with HHD. In study III, comparisons between HHD and PD were also performed.

Median survival for all cohorts and studies are given in table 6. Survival was significantly longer for patients starting with HHD compared with IHD in the

intention to treat analyses in both studies. The five-year survival was 98 % compared with 71 % in study II and 91 % compared with 70 % in study III (Figure 5) for patients with HHD and IHD, respectively.

In study III, a superior survival, according to intention to treat, was also reported for HHD compared with PD as initial RRT. The five-year survival was 76 % for patients starting with PD (figure 5).

In the cox regression analyses in study III, including the primary renal diagnoses as described above, HHD remained a factor associated with a favourable prognosis compared with both IHD ($p < 0.001$) and PD ($p = 0.033$), respectively. The hazard ratio was 0.55 (95 % CI 0.40-0.75) for HHD in the comparison with IHD and 0.70 (95 % CI 0.51-0.97) in the comparison with PD.

Survival was significantly longer for HHD compared with both IHD and PD, in the “on initial RRT analysis” in study III with censoring at all changes from the initial RRT (Table 6).

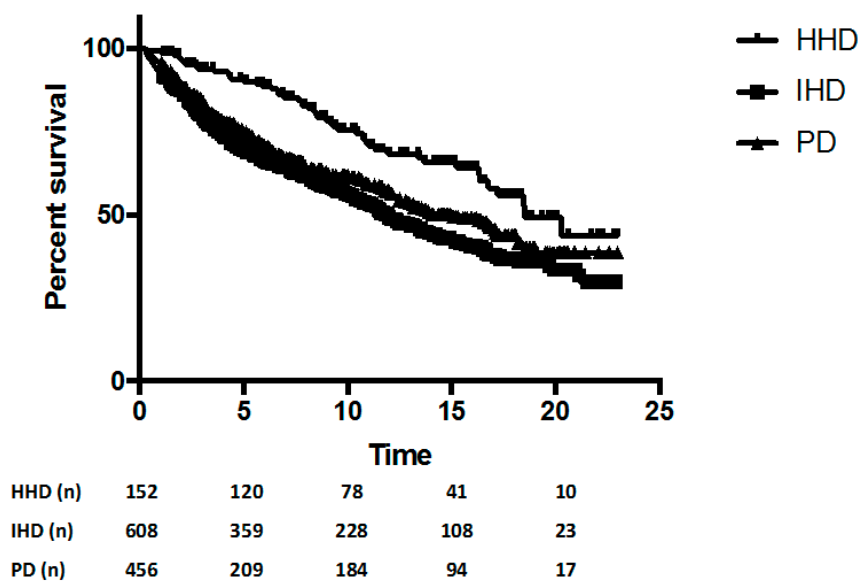


Figure 5
Superior overall survival (intention to treat analysis) for all Swedish patients with HHD as initial RRT during 1991-2012 compared with matched patients with IHD ($p < 0.001$) and PD ($p = 0.002$) as initial RRT (study III). In these analyses changes to other modalities were not considered and censoring was only performed at the end of the study

Comparison according to “on dialysis treatment”

Survival for patients with HHD and IHD were compared with “on dialysis treatment” analysis, without impact of subsequent renal transplantation, in studies II and III and between HHD and PD in study III. As seen in table 6, patients with

HHD still exhibited a significantly longer survival compared with IHD and PD after removal of the impact of renal transplantation.

Table 6
Survival for HHD patients and matched IHD and PD patients

Intention to treat					
<i>With censoring only at end of study</i>					
	Study II		Study III		
	HHD	IHD	HHD	IHD	PD
Median (IQR) years	16.7 (10.0-23.2)	11.2 (3.2-20.7)	18.5 (10.4-NA ¹)	11.9 (3.8- NA ¹)	15.0 (5.1- NA ¹)
Comparison with HHD (<i>p value</i>)	-	0.016	-	< 0.001	0.002
On initial RRT only					
<i>With censoring at all changes from the initial modality</i>					
	Study II		Study III		
	HHD	IHD	HHD	IHD	PD
Median (IQR) years	-	-	NA ² (8.4-NA)	6.3 (2.9-11.5)	6.1 (3.2-6.6)
Comparison with HHD (<i>p value</i>)	-	-	-	< 0.001	< 0.001
On dialysis treatment					
<i>With censoring at renal transplantation, recovered native renal function and end of study</i>					
	Study II		Study III		
	HHD	IHD	HHD	IHD	PD
Median (IQR) years	8.6 (6.8-NA ¹)	8.9 (3.0-10.8)	8.4 (6.7-10.7)	6.5 (3.0-11.5)	5.2 (3.1-6.6)
Comparison with HHD (<i>p value</i>)	-	0.015	-	0.001	< 0.001

¹ Not Available, survival > 25 % at end of follow up

² Not Available, survival > 50 % at end of follow up

Specific discussion

The advantages for HHD in comparison with IHD are similar to those reported for prevalent patients in Switzerland between 1970 and 1995[1], for incident patients in the US between 1986 and 1987[170], and for incident patients from Australia and New Zealand between 1996 and 2011[172, 173]. More recent studies from the US, one comprising incident patients between 1995 and 2004[174] and one comprising prevalent patients between 2005 and 2008[171], reported a disadvantage in survival or at least a less pronounced advantage for patients on HHD. The only studies with a long-term follow up during several decades similar to the studies in this thesis, are from Switzerland, Australia and New Zealand.

Previous comparisons between HHD and PD, have shown similar or more pronounced advantages for HHD. These reports come from Scotland between 1982 and 1988[175], from the UK for incident patients between 1997 and 2005[179] and from Australia and New Zealand for incident patients between

2000 and 2012[178]. In contrast, studies from the US comprising patients between 1995 and 2010, report no difference in survival[174, 176] for incident patients and a smaller reduction in mortality risk[176, 177] for prevalent patients compared with the results in this thesis. None of the studies comparing HHD with PD reported long-term survival.

The persisting advantage for HHD in the “on dialysis treatment” analyses in this thesis, without impact of subsequent renal transplantations, is in line with one previous study by Nesrallah et al. In that study, a survival advantage with a hazard ratio of 0.75 (95 % CI 0.68-0.82), was reported for prevalent patients with HHD compared with patients with PD[177].

Subsequent renal graft survival

Subsequent renal graft survival was compared between all Swedish patients starting HHD as initial RRT and matched patients starting IHD or PD in study III. There was no difference in graft survival between patients with HHD compared with IHD and PD as initial RRT in multivariable cox regression analyses. Ten year graft survival was 75 % for HHD (n=114), 72 % for IHD (n=313) and 75 % for PD (n=311) patients (p=0.416).

Specific discussion

To the author’s knowledge, this is the first study comparing renal graft survival subsequent to HHD and IHD or PD. There are two earlier studies reporting a similar decline in eGFR after renal transplantation subsequent to treatment with either HHD or IHD [187, 188], which is in line with the results in the present study.

Health care utilization

Health care utilization was compared between all Swedish patients starting HHD as initial RRT and matched patients starting IHD or PD in study IV, a retrospective observational registry-study.

All cause hospital admissions

Patients on HHD had a significantly lower admission rate of 1.7 times per year, compared with IHD with 2.2 and PD with 2.8. As seen in table 7, the median number of days in hospital was significantly lower and the median time to first admission was significantly longer for patients on HHD compared with IHD and PD.

These differences in health care utilization persisted even when including follow-up time after changes to other RRT in the intention to treat analyses. Patients on HHD had a significantly lower annual admission rate, fewer days in hospital and significantly longer time to first admission compared with IHD and PD.

Table 7

All cause hospital admissions during initial HHD/IHD/PD treatment only and during overall follow up

During initial HHD/IHD/PD treatment only					
	HHD	IHD	PD	HHD/IHD p value	HHD/PD p value
Patients % (<i>n</i>)	93 % (141)	94 % (573)	97 % (444)	-	-
Median annual admission rate [IQR] <i>n</i>	1.7 [0.9-2.8]	2.2 [1.1-4.4]	2.8 [1.3-5.3]	<0.001	<0.001
Median days per year [IQR] <i>n</i>	12.1 [6.6-21.4]	14.3 [6.4-33.3]	20.3 [9.3-41.2]	<0.001	<0.001
Median time to admission [IQR] years	0.7 [0.2-1.2]	0.3 [0.1-0.8]	0.4 [0.1-0.9]	<0.001	0.003
During overall follow up					
	HHD	IHD	PD	HHD/IHD p value	HHD/PD p value
Patients % (<i>n</i>)	97 % (147)	96 % (583)	99,6 % (454)	-	-
Median annual admission rate [IQR] <i>n</i>	1.3 [0.6-2.4]	1.6 [0.8-3.0]	1.5 [0.8-3.2]	0.014	0.023
Median days per year [IQR] <i>n</i>	6.5 [2.6-14.8]	8.5 [3.3-19.3]	8.9 [3.8-26.6]	0.048	0.001
Median time to admission [IQR] years	0.7 [0.2-1.2]	0.3 [0.1-0.8]	0.4 [0.1-0.8]	<0.001	0.001

Specific discussion

These results are in line with a previous study from Switzerland including patients treated with HHD or IHD between 1970 and 1995 and with a long-term follow up [1]. However, some recent studies, from the US and with a short-term follow up, did not show any differences in admission rates between HHD and IHD[192, 193]. Comparisons with PD have only been performed in the US and the results are divergent [176, 192, 194, 195]. In studies from the 21st century, restricted to incident patients, there was no difference in admission rates [176].

The annual number of admissions for all modalities was higher in study IV in this thesis compared with other studies. The European part of the DOPPS study reported an admission rate of around one for patients on IHD between 1998 and 2000[19]. The USRDS reported an annual admission rate for all dialysis patients of 2.1 during 2005, which decreased to 1.7 for IHD and 1.6 for PD during 2014[10]. In the recent studies from the US, comparing HHD with the other modalities, the admission rates were lower compared with our study, ranging from 0.7-1.8 for HHD, 1.1-1.7 for IHD and 0.7-1.9 for PD. These differences between the patients in this thesis and studies from other countries prevail in the number of days of hospital care per year, with lower numbers in other studies [176, 192, 193, 195]. The more frequent number of admissions in our study might partly be explained by a worse prognosis for patients on dialysis during earlier decades as we included patients from 1991 and onwards[8]. However, another important factor is the number of hospital beds per capita, which was higher in Sweden during the nineties compared with the US and the other European countries in the DOPPS study[213]. Finally, there might also be methodological differences. In the Swedish Inpatient Registry, new admissions are generated each time a patient is transferred to a new department during the same hospital stay.

Hospital admissions with cardiovascular diagnoses

Among all hospital admissions 14 % received a cardiovascular diagnosis and 24 % an infectious diagnosis, according to our definitions, while patients were still treated with their initial dialysis modality.

Although the majority of patients in all three cohorts did not have any admission with a cardiovascular diagnosis, while still on their initial RRT, HHD patients had a significantly lower median annual admission rate (HHD 0 IQR 0-0; IHD 0 IQR 0-0.4; $p=0.002$) as well as a longer period of time to first admission (HHD 6.1 years; IHD 4.8 years; $p=0.017$) compared with IHD patients. The significant advantage for HHD in the annual hospital admission rate did not persist in the intention to treat analysis. There were no significant differences between HHD and PD regarding admissions with a cardiovascular diagnosis.

Specific discussion

These results are in line with other studies reporting advantages for HHD compared with IHD, both for incident and prevalent patients[192, 193]. Some previous studies have shown an advantage for HHD compared with PD, but only in analyses including prevalent patients[176, 192], and not in those restricted to incident patients[176]. The divergent results for comparisons with prevalent or exclusively incident patients, are probably a reflection of the worse prognosis for patients on PD after 2-3 years on dialysis, with a declining residual renal function[173, 214-216].

The absence of differences in the intention to treat analyses was unexpected as the major cause of death for patients on dialysis is cardiovascular disease. A diminishing impact of the initial RRT after renal transplantation is a probable explanation. However, there might also be methodological concerns. The median admission rate with a cardiovascular diagnosis was low for all three cohorts of patients, analysed according to intention to treat, 0.06-0.07 per year in the present study, compared with 0.36-0.48, also analysed according to intention to treat, in the studies comparing HHD and IHD or PD by Weinhandl, and 0.5 per year as reported in the USRDS. Only 14 % of all admissions in the present study were assigned a cardiovascular diagnosis compared with 25 % in the USRDS[10].

The organization of the Swedish Inpatient Registry does not make it possible to discriminate between a cardiovascular event occurring during an admission from a chronic cardiovascular comorbidity, if it has not been assigned the position of principal diagnosis. Consequently, most cardiovascular ICD codes registered as secondary diagnoses could not be used in the classification of cardiovascular admissions in the present study, which most probably resulted in an underestimation of the number of admissions with a cardiovascular diagnosis.

Hospital admissions with infectious disease diagnoses

Regarding admissions with infections, patients with HHD had a significantly longer period of time to the first admission compared with IHD (HHD 3.4 years; IHD 2.8 years; $p=0.049$) with follow up according to “on initial RRT only”. There were no other significant differences between HHD and IHD. In comparison with PD, patients treated with HHD had a significant advantage as to annual admission rate (HHD 0 IQR 0-0.5; PD 0.3 IQR 0-1.5: $p<0.001$) and time to first admission (HHD 3.4 years; PD 1.3 years; $p<0.001$) with follow up according to “on initial RRT only”. These differences persisted, though were smaller, in the intention to treat analysis.

Specific discussion

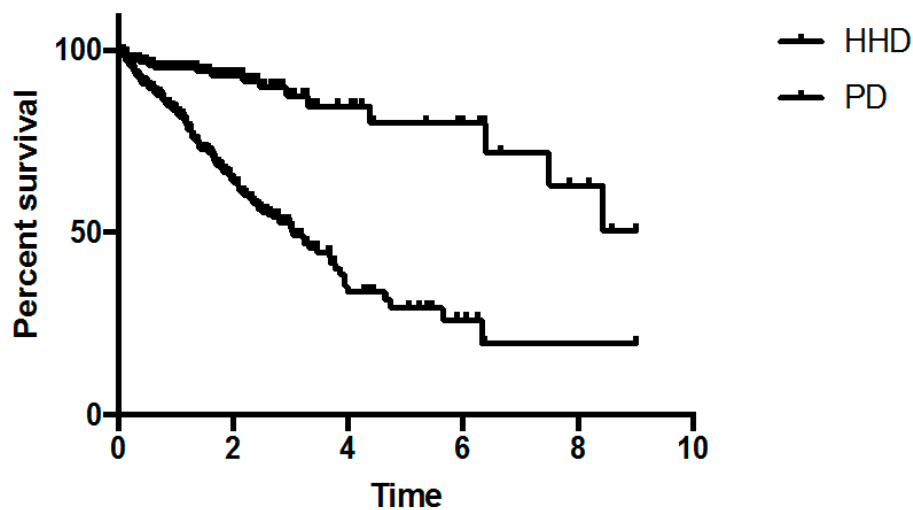
Other studies have, in accordance with our results, reported an advantage for HHD compared with PD[176, 192] in admissions with infectious diseases but contrary to our results, a disadvantage for HHD compared with IHD in admissions with infectious diseases[192, 193]. Sub-analyses in the study by Weinhandl, showed that blood-borne infections; bacteremia/sepsis, cardiac infection, osteomyelitis, and vascular access infection, were the main causes of the higher rate of admissions for HHD compared with IHD. Factors not analysed in the present study, might explain these differences between studies, such as the proportion of central dialysis catheters and arteriovenous fistulas and the quality of the patient education concerning access care. In addition, all patients on HHD in the studies by Weinhandl et al and Suri et al, had daily dialysis sessions, 5-6 times weekly, while the Swedish cohort of patients were prescribed different dialysis schedules and thus also had less frequent dialysis sessions.

Dialysis technique survival with HHD and PD

In study IV, technique survival, after censoring for death and renal transplantation, was found to be significantly longer for patients on HHD compared with PD ($p < 0.001$; figure 6). Median technique survival was 10.0 (IQR 6.4–not available) years for patients on HHD and 3.0 (IQR 1.3-6.3) years for PD. Two and five year' technique survival was 93 % and 80% for HHD and 64 % and 29 % for PD, respectively. During follow up, 18 patients on HHD (12 %) changed to IHD and 151 (33 %) patients on PD changed to IHD and one changed to HHD.

Specific discussion

The two-year technique survival is in line with other studies from the US, Europe, Australia and New Zealand, reporting 75-96 % for incident HHD patients and 64-74 % for incident PD patients, but with figures in the higher range for HHD and in the lower range for PD. The improved dialysis technique survival for HHD is probably a contributing factor to the lower admission rate for patients with HHD.



HHD (n)	152	72	25	13	7
PD (n)	456	130	22	8	3

Figure 6
Superior dialysis technique survival for all Swedish patients treated with HHD as initial RRT between 1991 and 2012 compared with matched patients with PD as initial RRT ($p < 0.001$; study IV). In this analysis censoring was performed at dates of renal transplantation, the end of study and dates of death. Only changes to other dialysis modalities were defined as events.

Modifiable risk factors associated with hemodialysis treatment

Dialysis accesses

In study II, 76 % of the patients on HHD had an AV fistula or graft at start of HHD compared with 46 % of the patients on IHD ($p = 0.008$). At 18 months after start of HHD or IHD (or at a switch to another dialysis modality or renal transplantation before 18 months), 93% compared with 76 % patients, respectively, had an AV fistula or graft ($p = 0.39$).

Specific discussion

Even though the difference in the frequency of AV fistulas or grafts between patients on HHD or IHD in study II was smaller and non-significant at 18 months after start of HHD or IHD, the higher frequency of a persistent dialysis catheter might contribute to the worse survival in patients on IHD compared with HHD.

Dialysis dose

As seen in table 8, the dialysis doses for HHD in studies I and II, were higher compared with CHD. In study I, the median weekly duration of dialysis 6 and 12 months after start of HHD was 15 hours and 16 hours, respectively.

In study II, the median weekly duration of a dialysis session was significantly longer for HHD compared with IHD, both at 6 ($p<0.001$) and 18 months after start ($p=0.001$). At 6 and 18 months the median duration was 15 hours and 15.5 hours, respectively, for patients on HHD compared with 12 hours for patients on IHD at 6 and 18 months.

Specific discussion

Several previous studies have reported improved survival with more intensive dialysis schedules[29, 40, 41, 48, 50, 51, 53]. The higher dialysis dose for patients with HHD is probably one of the most important explanations for the improved prognosis.

Table 8
Dialysis doses

	Study I		Study II				P value (n)	
	HHD		HHD		IHD			
Months after start	6	12	6	18	6	18	6	18
Dialysis duration per week Median (min-max range)	15 (8-30)	16 (9-30)	15 (10.5-38.5)	15.5 (12-28)	12 (8-15)	12 (8-15)	<0.001 (28)	0.001 (14)
Dialysis frequency per week Median (min-max range)	3 (2-3.5)	3 (2-4)	3 (3-6)	3 (3-4)	3 (2-3)	3 (3-3)	0.005 (28)	0.066 (14)

All values are given as median (minimum-maximum range)

Modifiable risk factors inherent in CKD

Modifiable risk factors inherent in CKD were compared between patients starting HHD as initial RRT at Lund University Hospital and matched patients starting IHD at Malmö General Hospital in study II, a retrospective observational study based on data from patient records.

Fluid balance and blood pressure

As seen in table 9, patients on IHD had a significantly higher number of antihypertensive drugs, including diuretics, based on ATC codes both at 6 (<0.001) and 18 months ($p=0.014$) after start of HHD or IHD.

Mean blood pressure at 6 and 18 months was 141/81 and 149/82, respectively, for patients on HHD and 151/86 and 150/84, respectively, for patients on IHD. As the recording of blood pressure was performed under different circumstances for patients on HHD and IHD, no statistical analysis was conducted.

Table 9
Antihypertensives and diuretics

	HHD		IHD		P value		n	
	6	18	6	18	6	18	6	18
Months after start	6	18	6	18	6	18	6	18
Number of antihypertensives and diuretics	0 (0-3)	0 (0-3)	2 (0-5)	2 (0-5)	<0.001	0.014	26	10
Number of antihypertensives only	0 (0-2)	0 (0-3)	2 (0-4)	2 (0-4)	0.002	0.037	26	10
DDD antihypertensives	0 (0-4)	0 (0-2.4)	1.3 (0-5.2)	1.2 (0-5.7)	0.11	0.21	24	9
DDD diuretics	0 (0-13)	0 (0-13)	6.3 (0-25)	3.1 (0-25)	0.007	0.043	26	10

All values are given as median (minimum-maximum range)

Specific discussion

Previous studies in dialysis patients have shown associations between mortality and blood pressure, fluid overload, high ultrafiltration volumes and left ventricular hypertrophy[72-74]. As these factors were not available for all patients or not measured in a standardized manner, we used prescriptions of antihypertensive drugs and diuretics as markers of the fluid balance and blood pressure. Indirectly, the results of this study indicate an improvement in fluid balance and blood pressure for patients on HHD compared with patients on IHD. Randomized controlled studies have shown improved blood pressure [35, 56, 88], decreased left ventricular hypertrophy[35, 88] and a reduction in the prescribed antihypertensives[56] with a more intensive dialysis schedule, NHD[56, 88] or SDHD[35], compared with CHD. In addition, an improvement in interdialytic weight gains, has been reported for patients on hemodialysis randomized to a cognitive behavioural intervention and education about fluid balance compared with patients with standard care[70]. Thus, both an increased dialysis dose and patient education might have an impact on fluid balance and blood pressure for patients on HHD.

Phosphate and calcium

Patients on HHD have significantly lower mean-time averaged plasma phosphate levels during the period 6-18 months after start, 1.5 +/- 0.26 mmol/L, compared with patients on IHD, 2.1 +/- 0.56 mmol/L (p<0.001). There was no difference in mean plasma calcium (p=0.33) or in the number of prescribed phosphate binders,

according to ATC codes, at either 6 or 18 months between patients on HHD or IHD ($p=0.74$, $p>0.99$).

Specific discussion

The lower phosphate levels reported for patients on HHD are probably caused both by an increased dialysis dose and patient education, typical characteristics of HHD, and both previously shown to have an impact on phosphate levels[68]. Several randomized controlled studies have shown improved phosphate levels[35, 56, 88, 104] or a reduced number of prescribed phosphate binders[88, 103, 104] with more intensive dialysis schedules, NHD or SDHD, compared with CHD. The improvement in phosphate, in these studies, is more pronounced for patients on NHD, 0.4-0.5 mmol/L, compared with the improvement reported for patients on SDHD, 0.1-0.2 mmol/L.

In congruence with our results, most randomized controlled studies[88, 103] report unchanged calcium levels for NHD or SDHD compared with CHD. PTH levels could not be compared between HHD and IHD because of the multitudes of assays used during the study period and a sparsity of measurements. However, no difference in PTH has been reported in the randomized controlled studies investigating different dialysis schedules[88, 103, 104].

Plasma albumin and renal anemia

There was no significant difference in mean-time averaged plasma albumin during the period 6 -18 months after start between patients on HHD or IHD ($p=0.56$).

There were no significant differences, in the mean-time averaged blood hemoglobin concentration, although there was a trend towards higher mean levels for the patients on HHD, 106 g/L compared with 102 g/L ($p=0.33$). There were no significant differences in prescribed doses of ESA per week at 6 months after start of HHD or IHD ($p=0.078$). However, at 18 months, the patients on HHD had significantly higher doses ($p=0.038$), 7700 IE per week compared with 3010 IE per week for the IHD patients. Prescriptions of iron were not analysed due to a lack of clear documentation of prescriptions in the patient records.

Specific discussion

The absence of significant differences in albumin levels between HHD and IHD is in line with previous randomized controlled studies comparing NHD or SDHD with CHD[35, 56].

Albeit that there are previous observational studies reporting higher hemoglobin and reduced ESA doses for patients with longer duration of the dialysis session or a more intensive dialysis schedule compared with CHD[128-132] the results in

randomized controlled studies comparing NHD or SDHD and CHD are congruent with our results and do not reveal any significant differences in haemoglobin concentration or dose of erythropoiesis stimulating agents[35, 56, 88, 103, 135].

General discussion

Improved prognosis with HHD

The studies in this thesis show an improved long-term prognosis for patients treated with HHD as initial RRT compared with patients treated with IHD or PD. These findings were beyond differences in patient selection between the modalities. The median survival for patients starting HHD was 17 and 19 years, respectively, compared with 11 and 12 years for patients on IHD, as shown in studies II and III, and 15 years for patients on PD, as shown in study III. The hospital admission rate was 65 % higher for patients on IHD and 33 % higher for patients on PD compared with HHD. In addition, patients starting HHD had a longer median dialysis technique survival, 10 years, compared with 3 years for patients starting PD. Subsequent renal transplantation was most frequent in patients starting HHD. There was no difference in subsequent renal graft survival after HHD and IHD or PD.

There are previous studies in these fields, but most have shorter periods of follow up. However, the effects of HHD and IHD or PD, respectively, on renal graft survival is novel information. Even though most studies report an advantage in survival and health care utilization for HHD, the magnitude of this difference varies between countries and decades. Interestingly, some studies did not find an advantage or even report a disadvantage for HHD.

Reasons for the improved prognosis

Patients with HHD are younger, have less comorbidities and are more prone to receive a renal transplant compared with patients on other dialysis modalities. It is noteworthy, that this thesis shows that patient selection and subsequent renal transplantation are not sufficient explanations for the superior prognosis for HHD compared with IHD and PD. The improved long-term prognosis for HHD compared with IHD and PD persisted after strict matching for sex, age, validated comorbidity indices and date of start of RRT.

In patients younger than 60 years with no comorbidities a subsequent renal transplant had no major influence on patient survival (study I). It is interesting, that a substantial advantage in survival for patients on HHD as initial RRT

persisted, 8.4 years for HHD compared with 6.5 years for IHD and 5.2 years for PD, in the “on dialysis treatment” analyses i.e. without impact of subsequent renal transplantation (Studies II and III).

In consequence, factors related to the dialysis modality per se must have a major impact on prognosis. Increased dialysis dose and more patient education are important characteristics of HHD. Both these factors are related to improved survival according to several observational and randomized controlled studies.[29, 40, 41, 50, 53, 61, 66, 67] For the patients starting HHD in Lund between 1971 and 2002, the median weekly duration of dialysis was 16 hours 12-18 months after start of HHD (Studies I and II). Even though the weekly duration with NHD is longer, the patients in these studies had a substantially longer duration than CHD. For all patients starting HHD at Lund University Hospital, there was a standardized educational program during a period of 2-3 months with a specialized nurse, who gave the patients extensive instruction on hemodialysis and chronic kidney disease. Unfortunately, data on patient education and dialysis dose were not available for the entire Swedish cohort of patients with HHD in studies III and IV.

It is of importance to note, that previous randomized controlled and observational studies have shown that patient education and an increased dialysis dose improve important prognostic factors related to cardiovascular morbidity and to mortality for patients on dialysis[35, 56, 57, 88, 103, 104]. Patients starting HHD had a significantly lower number of antihypertensive medications and diuretics (study II). This indicates indirectly an improved fluid balance and blood pressure. Moreover, the patients on HHD had significantly lower levels of plasma phosphate, despite similar amounts of phosphate binders (study II). As all these factors are known to affect cardiovascular morbidity, these effects could contribute to the decreased admission rate with cardiovascular diagnoses for HHD compared with IHD (study IV). Patients on HHD and PD showed no difference in admission rate with cardiovascular diagnoses, but for infectious disease diagnoses there was a significant advantage for patients on HHD (study IV). These are interesting findings, as both cardiovascular and infectious morbidity affect the overall prognosis being the most important causes of death for patients on dialysis.

The results presented in this thesis are in accordance with some studies, but diverge from some recent studies from the US, which reported fewer pronounced advantages for HHD. It is noteworthy, that all the patients on HHD in these studies were treated with a special low-dialysate flow dialysis device. This dialysis device was not approved in Sweden until 2010. To date, it still does not constitute the majority of HHD dialysis devices used in Sweden. In order to achieve an adequate dialysis dose with this device, a longer weekly duration of dialysis is required. This device is also less complicated and the training period is usually shorter.

Thus, differences in dialysis dose and patient education persist as two possible factors explaining why results from certain studies are different from those in this thesis. Other factors, which could have an impact on the differences between studies and countries, are the organization of dialysis care, the allocation of patients to different modalities, the methodological treatment in the studies of differences in patient selection between modalities, decade of inclusion and length of follow up.

Limitations and strengths

Because of the retrospective design of the studies in this thesis, there are a number of limitations. The major limitation, is that despite strict matching, there is still a risk of residual confounding for instance in smoking and socioeconomic factors. However, these confounding factors should be evenly spread. As the health care system in Sweden is publicly funded, access to different RRT modalities is relatively homogenous for all citizens. Even though diabetes mellitus was included in the comorbidity indices, differences in the numbers of patients with diabetic nephropathy as a primary renal diagnosis, might still have an impact on differences in outcome between the cohorts.

Missing information

Information about dialysis accesses was available in study II and information about dialysis prescriptions was available in studies I and II. However, it would have been useful to have this information in all studies. Information on residual renal function and prognostic laboratory measures at start of dialysis was not available in any of the studies. There was no information about self-care dialysis in IHD in the data retrieved from the SRR. Since 2003, this information is reported in the annual cross-sectional surveys in the SRR. The proportion of self-care among all patients on hemodialysis, was below 3 % until 2008 after which it rose to 8 % in 2012 and 2013, the last years of follow up in the studies in this thesis.

Limitations in separate studies

Fluid balance and hypertension could only be compared through surrogate measures, such as prescriptions of antihypertensive drugs and diuretics, and not as inter-dialytic weight gain, ultrafiltration rate, standardized measures of blood pressure or left ventricular mass. The prescriptions of phosphate binders could only be compared as a quantitative measure and not as a phosphate binding index[217]. Albumin was the only marker of inflammation available as a laboratory analysis (study II). Hospital admissions with cardiovascular diagnoses are probably underestimated due to the organization of the Inpatient Registry as described above (study IV).

Merits

The studies also have important merits. The cohorts with HHD, IHD and PD were strictly matched according to several factors, including validated comorbidity indices. Moreover, due to the long tradition with high quality registries in Sweden, it was possible to follow patients for two or three decades in all studies. All Swedish patients starting HHD as initial RRT during the study period could be included in studies III and IV, because of a coverage of nearly 100 % in the SRR, the Swedish Inpatient Registry and the Swedish Mortality Database.

Future perspectives

The results of the studies in this thesis are strong incentives for promoting the use of HHD with the objectives of increasing survival and decreasing morbidity in patients on maintenance dialysis. It is noteworthy, that an increased use of HHD is economically feasible as it has a lower cost than IHD and to some extent also compared with PD[218, 219]. Thus, the main challenges to increase the use of HHD are to inform financial decision makers, health care personnel and patients about the advantages of HHD. Available HHD units and sufficient resources for patient education are a prerequisite and patients must also be given the opportunity to choose HHD treatment by their physicians and nurses. One important tool is timely referral to a Nephrology clinic, so that patient education can be offered during the pre-dialysis phase, which has been shown to increase the proportion of patients choosing self-care dialysis[61, 62].

Despite the strong advantages for HHD shown in this thesis, there are still important and interesting questions that remains to be answered:

Is decreased cardiovascular morbidity the main reason for the improved long-term survival in patients treated with HHD compared with other dialysis modalities? Which are the most important modifiable risk factors with impact on survival for this young and otherwise healthy subgroup of patients starting dialysis?

Cardiovascular disease is the most important cause of death for patients with dialysis according to renal registries[8, 10, 13]. In this thesis, we showed superior survival and decreased frequency of admissions with a cardiovascular diagnosis for patients, on their initial RRT, treated with HHD compared with patients treated with IHD. However, in the intention to treat analyses, there was no difference in admissions with a cardiovascular diagnosis for patients treated with HHD compared with patients treated with PD or IHD. This raises the question whether a lower incidence of cardiovascular disease or of other diseases are the main reasons for the superior long-term survival in patients on HHD. The next question is what modifiable risk factors are the most important contributors to the decreased mortality for this subgroup of young and otherwise healthy patients? This knowledge could be used with the intent of improving survival for young and otherwise healthy patients on all dialysis modalities.

How is the quality of life for patients on HHD compared with other RRT?

Differences in self-reported measures of quality of life between HHD and IHD or PD is as yet not fully elucidated. There are some previous studies reporting divergent results in comparisons between HHD and IHD; improved measures in studies from Japan[220] but no significant differences in studies from Finland[221] or Sweden[222]. Patient-related outcome measures, using the RAND-36, have recently been added to the SRR, enabling comparisons of quality of life between patients on HHD and IHD or PD in the future.

What is the employment rate, the frequency of disability pensions and work income for patients on HHD compared with other RRT?

There are not many studies on socioeconomic outcomes for patients treated with HHD. Higher employment rates have been reported for Chinese patients on nocturnal HHD compared with patients on PD[223] and for Finnish patients on HHD compared with patients on IHD[224]. In an unpublished report by Johan Jarl et al at the request of the Swedish Kidney Federation (Njurförbundet), the employment rate for Swedish patients on HHD was found to be higher compared with patients on IHD[225]. It would be of interest to explore socioeconomic perspectives of HHD treatment compared with other RRT both from the viewpoint of the individual patient and for society.

Are access-related events more common in patients treated with HHD compared with IHD?

Previous studies from the US and Canada, have reported higher risk of dialysis-access-related events for patients with AV fistulas or AV grafts treated with frequent hemodialysis performed either in-center[226] or at home[56, 171, 192] compared with CHD. Whether there is a difference in the frequency of access-related events between HHD and IHD in Sweden, with a different praxis of dialysis is not known. Should there be a difference, the next question would be whether it is related to frequency, self-administration, differences in surveillance of accesses between modalities or other factors.

When and for how long should patients have PD if used in an integrated home-dialysis model?

There is a rising interest in an integrated home-dialysis model, in which patients start on PD, and then continue on HHD, because of complications or insufficient dialysis with PD. A study from Australia and New Zealand compared the combined patient and home-dialysis technique survival, defined as a transfer to IHD, between patients only treated with PD, only treated with HHD or treated first with PD and then transferred to HHD[227]. The outcome was similar for patients only treated with HHD and patients with PD first who then transferred to HHD,

while both groups had a superior outcome compared with the patients only treated with PD. As the results in this thesis are not fully congruent with the results from Australia and New Zealand, further studies are needed to answer when and for how long patients should have PD.

*Are there advantages, in hospital admission rates, dialysis technique survival, quality of life or patient survival, in patients treated with assisted PD compared with IHD for the oldest patients with most comorbidities?
What is the financial cost for assisted PD compared with IHD?*

It would be interesting to study assisted home-dialysis, for the oldest patients with most comorbidities. Assisted HHD is not available in Sweden today. There are only a few previous studies in this field. One study which included patients older than 65 years, with self-administered HHD or assisted HHD, reported lower hospital admission rates and mortality compared with all patients on dialysis in renal registries[228]. Assisted PD is available in Sweden and the number of patients is rising. Two previous studies, one from Canada and one from the UK compare assisted PD with IHD and report similar frequencies of hospital admissions[229] and similar quality of life[230], However, in Canada, assisted PD is performed either by relatives or by health care personnel and not solely by health care personnel as in Sweden.

Conclusions

- Survival in patients on HHD was superior compared with survival in the whole Swedish cohort of patients on dialysis (studies I and III).
- Non-modifiable factors with a significant impact on survival were age, comorbidity and decade of start of HHD. Subsequent renal transplantation did not have a significant impact on survival for the younger patients without comorbidities (study I).
- The survival benefit was beyond patient selection for patients treated with HHD compared with IHD and PD (studies II and III).
- Renal transplantation was more common in patients with HHD compared with IHD and PD. HHD as initial dialysis modality had no impact on graft survival after subsequent renal transplantation (study III).
- Morbidity, measured as hospital admissions, was lower for patients treated with HHD compared with IHD or PD. Patients on HHD seemed to have less cardiovascular morbidity compared with patients on IHD and less infectious morbidity compared with patients on PD, as the admission rates were lower for these diagnoses in patients on HHD. Dialysis technique survival was superior for HHD compared with PD (study IV).
- Possible causes for the superior survival and decreased morbidity were lower phosphate levels, improved fluid balance and blood pressure, measured indirectly by number of medications, for patients on HHD compared with IHD (study II).

Popularized scientific summary in Swedish

Bakgrund

Varje år i Sverige startar drygt 1000 nya patienter dialys eller får ett njurtransplantat då deras egna njurfunktion upphört. Totalt lever idag nästan 10 000 patienter i Sverige med kronisk dialysbehandling eller ett fungerande njurtransplantat. Majoriteten av patienterna har ett fungerande njurtransplantat, 58 %. Av dialysbehandlingarna är bloddialys på sjukhus, så kallad institutionshemodialys, vanligast (32 %) följt av peritonealdialys, även kallat påsdialys (9 %). En liten minoritet av patienterna (1 %) sköter själva sin bloddialys i hemmet, så kallad hemhemodialys.

Den årliga dödligheten är hög för patienter i dialys även om den har minskat från 30 % 1991 till 18 % 2016. Dödligheten för njurtransplanterade patienter har varit betydligt lägre under hela perioden, 3 % under 1991 med en sjunkande trend till 2.5 % under de senaste åren. De vanligaste dödsorsakerna för patienter med dialys är hjärt- och kärlsjukdomar följt av infektionssjukdomar. Detta avspeglas även i sjuklighet. Hälften av sjukhusinläggningarna för patienter i dialys beror på hjärt- och kärlsjukdomar och infektionssjukdomar.

Flera olika faktorer som hör ihop med dialysbehandlingen eller med njursvikten påverkar sjuklighet och dödlighet. Hur mycket dialys och patientutbildning som ges samt vilken typ av dialysaccess som används för att få tillgång till blodbanan vid bloddialys har betydelse för prognosen. Njursvikten i sig påverkar prognosen via påverkat blodtryck och vätskebalans, ökad inflammation, ansamling av fosfat och andra uringifter och påverkad syra-basbalans. En avtagande egen urinproduktion är också relaterat till sämre överlevnad.

Tidigare studier har visat att patienter med hemhemodialys lever längre än patienter med annan typ av dialys. Viktiga egenskaper för hemhemodialys är patientutbildning och hög dialysdos, faktorer som påverkar överlevnaden positivt. Patienter som har hemhemodialys är dock yngre och friskare jämfört med hela gruppen av patienter med dialys vilket också påverkar överlevnaden. Det är inte klarlagt i vilken utsträckning dialyssorten i sig bidrar till den förbättrade prognosen, och i så fall varför.

Syfte med avhandlingen

- Att undersöka överlevnaden för svenska patienter som startar hemhemodialys som första typ av aktiv uremivård (studie I, III)
- Att analysera vilka icke modifierbara faktorer som påverkar överlevnaden (studie I)
- Att studera om överlevnaden är längre för patienter med hemhemodialys jämfört med patienter med institutionshemodialys eller peritonealdialys då hänsyn tagits till dessa faktorer (studie II och III)
- Att studera vilken effekt hemhemodialys, som första typ av dialys, har jämfört med institutionshemodialys och peritonealdialys, på hur länge njurtransplantat fungerar vid efterföljande transplantationer (studie III)
- Att jämföra sjuklighet, uppmätt som frekvens av sjukhusinläggningar, mellan hemhemodialys och institutionshemodialys respektive peritonealdialys (studie IV)
- Att undersöka hur hemhemodialys påverkar kända riskfaktorer jämfört med institutionshemodialys (studie II)

Metod

Studiepopulationen i studie I utgjordes av alla patienter som startat hemhemodialys som första typ av aktiv uremivård (dialys eller njurtransplantation) vid universitetssjukhuset i Lund 1971-1998. I studie II matchades patienter som startat hemhemodialys i Lund 1983-2002, med patienter som startat institutionshemodialys på Malmö allmänna sjukhus. I studie III och IV jämfördes alla svenska patienter som startat hemhemodialys 1991-2012 med matchade patienter som startat institutionshemodialys och peritonealdialys.

Matchning gjordes med avseende på kön, ålder, annan sjuklighet och datum för start av aktiv uremivård. I studie I och II hämtades uppgifter från patientjournaler. I studie III och IV hämtades uppgifter från svenskt njurregister och från socialstyrelsens patientregister.

Resultat

Den årliga dödligheten för patienter som startat hemhemodialys i Lund var 4.9 %. (studie I)

Högre ålder, annan sjuklighet och start av hemhemodialys under senare årtionde var relaterat till sämre överlevnad. Kön och typ av njursjukdom var inte relaterat

till överlevnad. För yngre patienter utan annan sjuklighet påverkade inte efterföljande njurtransplantationer överlevnaden. (studie I)

Medianöverlevnaden för patienter som startat hemhemodialys var längre, 18.5 år, jämfört med för matchade patienter som startat institutionshemodialys, 11.9 år, och peritonealdialys, 15.0 år, även då hänsyn tagits till ovanstående faktorer. (studie III)

Patienter med hemhemodialys hade större chans att bli njurtransplanterade, men det var ingen skillnad i tiden som njurtransplantat fungerade vid transplantationer efter hemhemodialys som första typ av dialys jämfört med institutionshemodialys eller peritonealdialys. (studie III)

Patienter med hemhemodialys hade mindre sjukvårdskonsumtion, uppmätt som totalt antal sjukhusinläggningar, jämfört med patienter med institutionshemodialys och peritonealdialys. Hemhemodialyspatienterna hade färre sjukhusinläggningar orsakade av hjärtkärlsjukdom jämfört med institutionshemodialys och färre sjukhusinläggningar orsakade av infektionssjukdomar jämfört med patienter med peritonealdialys. De kunde också fortsätta med sin behandling under längre tid jämfört med patienter i peritonealdialys, utan behov av byte till annan dialysform. (studie IV)

Bland tänkbara förklaringar till den bättre prognosen kunde konstateras att patienter med hemhemodialys hade förbättrad vätskebalans och bättre blodtryck, uppmätt indirekt genom färre blodtrycksmediciner och vätskedrivande mediciner, och lägre fosfatvärden jämfört med patienter med institutionshemodialys. (studie II)

Sammanfattning

Patienter med hemhemodialys har bättre långtidsprognos, längre överlevnad, större chans att bli transplanterade och mindre behov av sjukhusvård, jämfört med patienter som startat institutionshemodialys eller peritonealdialys, även då hänsyn tagits till skillnader i patienturval mellan de olika dialyssorterna. Resultaten utgör starka motiv för en ökad användning av hemhemodialys med syfte att ge patienter utan egna fungerande njurar ett längre och friskare liv.

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Paper I



Excellent long time survival for Swedish patients starting home-hemodialysis with and without subsequent renal transplantations

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Abstract

Survival for patients on dialysis is poor. Earlier reports have indicated that home-hemodialysis is associated with improved survival but most of the studies are old and report only short-time survival. The characteristics of patient populations are often incompletely described. In this study, we report long-term survival for patients starting home-hemodialysis as first treatment and estimate the impact on survival of age, comorbidity, decade of start of home-hemodialysis, sex, primary renal disease and subsequent renal transplantation. One hundred twenty-eight patients starting home-hemodialysis as first renal replacement therapy 1971–1998 in Lund were included. Data were collected from patient files, the Swedish Renal Registry and Swedish census. Survival analysis was made as intention-to-treat analysis (including survival after transplantation) and on-dialysis-treatment analysis with patients censored at the day of transplantation. Ten-, twenty- and thirty-year survival were 68%, 36% and 18%. Survival was significantly affected by comorbidity, age and what decade the patients started home-hemodialysis. For patients younger than 60 years and with no comorbidities, the corresponding figures were 75%, 47% and 23% and a subsequent renal transplantation did not significantly influence survival. Long-term survival for patients starting home-hemodialysis is good, and improves decade by decade. Survival is significantly affected by patient age and comorbidity, but the contribution of subsequent renal transplantation was not significant for younger patients without comorbidities.

Keywords: Comorbidity, home-hemodialysis, dialysis, renal transplantation, survival

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INTRODUCTION

The overall survival for patients with end-stage renal failure is poor. The annual mortality in Sweden between 1991 and 2010 for patients on renal replacement therapy was 13% and for those treated with dialysis 26% according to Swedish Renal Registry (SNR). There are several reports indicating that home-hemodialysis (HHD) is associated with an improved prognosis compared to other modalities of dialysis.^{1–19} Albeit, many of these studies are dated with inclusion during the sixties and seventies.^{1–4,8,12,15,20–22} Not many of the earlier studies have defined patient populations with respect to comorbidity and age. In other studies, few patients have been followed for more than 5 years.^{1,4,8,9,15} Some studies stop following patients when they are transferred to other treatment modalities.^{1,2,4,5,8,20,21} To stop following patients after changing to in-center hemodialysis most probably overestimates survival of HHD patients, since patients acquiring severe comorbidities are less likely to continue home treatment. On the other hand, to stop following patients after transplantation would probably underestimate survival. Furthermore, survival figures differ substantially between countries and over time. While reported 1 year mortality figures from North America range between 2% and 16%^{1–5,8,10,20,21} figures from Europe tend to be lower, 2%–4%.^{6,9,11,13,16} Some other studies do only analyze the combined patient and technique survival.^{23,24} When advising young and middle-aged patients approaching the need for dialysis today, we still have insufficient knowledge of the long-term prognosis and whether it can be modified by choice of treatment modality.

The HHD program at Lund University Hospital was initiated by the dialysis pioneer Nils Alwall and his colleagues in 1971. Patients are recruited from a catchment area in southern Sweden. Home-hemodialysis has been considered to be a treatment of choice for those patients who cannot receive a renal transplant within the near future. The Swedish census and SNR enable us to follow patients also after a switch of treatment modality.

The aim of this study was to analyze long-time survival for patients starting HHD as first treatment and to estimate the contribution of patient age, comorbidity, decade of start of HHD, sex, renal diagnosis as well as subsequent renal transplantations.

MATERIALS AND METHODS

Patients were referred to the HHD program from the tertiary referral area for Lund University Hospital with a population of 1.4 million in 1971 and 1.6 million in 1998.

The incidence of dialysis in Sweden rose from 16 per million to 123 per million during this period. There were no strict selection criteria for referral or acceptance to HHD training but an individual assessment for each patient by each physician. The selection of patients has changed over time.

The first patient started training for HHD at the Department of Nephrology, Lund University hospital on December 13, 1971. All patients starting HHD training from that date were eligible for this study, if HHD was the initial modality of renal replacement therapy. Home-hemodialysis as initial modality was defined as starting training within 6 months of any kind of dialysis or transplantation attempt. To allow a minimum of 10 years of follow-up, only patients starting before January 1, 1999 were included in the study. Out of 186 patients commencing training during that period, 128 fulfilled the definition for HHD as first treatment.

Data about patient age, comorbidity, sex and renal diagnosis at start of HHD were collected from patient files. Comorbidity was recorded using Davies Index.^{25–27} In Davies index, grade 0 represents low mortality risk, grade 1 medium risk and grade 2 high risk.

Date on start of the first day of renal replacement therapy, start of HHD training, changes between renal replacement therapies and death were collected from patient files, SNR, the transplant registry for southern Sweden and the Swedish census. All patients were followed until December 31, 2008 and no patient was lost to follow-up.

Data on weekly dialysis duration and frequency were recorded from patient files at 6 and 12 months after start of HHD. For 110 patients, complete data were found at 6 months. For 79 patients, complete data were found at 12 months.

The day for start of HHD training was used as day zero in the survival analyses. Home-hemodialysis training comprised 2–3 months with a specialized nurse, who taught the patients all aspects of hemodialysis and chronic kidney disease (CKD) according to a standardized educational program. During the training period, the patient received four dialysis sessions per week at the HHD clinic.

Survival analysis was made for all 128 patients both as an intention-to-treat analysis and on-treatment analysis. In the intention-to-treat analysis, patients were considered still at risk also after changes to other modalities of renal replacement therapy, including transplantation. In the on-treatment analysis, patients were censored as “lost to follow-up” on the day of renal transplantation. However, patients were not censored when changing to other

dialysis modalities such as in-center hemodialysis or peritoneal dialysis. For one patient, the day of renal transplantation could not be retrieved. He was censored the day he left HHD in the on-treatment analysis.

For comparison, data on age and survival were collected from SNR for all incident patients with renal replacement therapy during the same period.

Statistical analysis was performed with IBM SPSS version 19. For survival analysis, Kaplan–Meier curves and log rank test (Mantel–cox) were used for calculation of statistical differences. Multiple regression analysis was performed with Cox proportional hazard method. For calculation of other statistical differences between groups of patients, chi-square test, Mann–Whitney and Kruskal–Wallis were used. Age was assumed not to have a normal distribution.

The study is approved by the Regional Ethical Review Board in Lund. The patients are informed about the study by letter. Informed consent was not required or recommended for approval.

RESULTS

During the period of 1971–1998, 128 patients, 93 men and 35 women, started HHD at our center, with HHD as initial renal replacement therapy. The median age when starting HHD was 46 (range 16–71) years. When starting HHD, 103 patients (80%) had Davies comorbidity grade 0. Twenty-four patients (19%) had comorbidity grade 1 and only one patient (0.8%) had comorbidity grade 2. The most common renal diagnosis was glomerulonephritis (42%) followed by adult polycystic kidney disease (26%),

chronic interstitial nephritis (13%) and nephrosclerosis (7%). Only one patient had diabetic nephropathy. Sixty-two patients started HHD 1971–1979. Forty-three patients started 1980–1989 and 23 patients started 1990–1998 (Table 1).

The majority of the patients had their first dialysis session at the HHD training clinic, but 52 patients (41%) had a short period with in-center hemodialysis or peritoneal dialysis before starting HHD. The median time for that period was 51 days (range 2–176). In addition, five patients started HHD training within 6 months of a failed transplantation attempt. The median time from renal transplantation to start of training was 72 days (range 48–159).

The median weekly duration of dialysis 6 months after start of HHD was 15 hours (range 8–30). The mean weekly duration was 17 hours. The corresponding figures 12 months after start of HHD were 16 hours (range 9–30) and 17 hours. The mean frequency per week at 6 and 12 months after start of HHD was 3.0. The median frequency per week at 6 and 12 months were three (range 2–3.5 and 2–4, respectively).

Total survival

All patients were followed from the start of HHD training until January 1, 2009. At that date, 40 patients were still alive. No patient died during the training period. The overall 5-year survival was 84%, while the figures for 10, 15, 20 and 30 years were 68%, 52%, 36% and 18%, respectively. (Figure 1A) The annual mortality for the first 20 years was 4.9%.

Table 1 Patient characteristics during different decades

	Total	1971–1979	1980–1989	1990–1998
Patients n	128	62	43	23
Median age (range) years	46 (16–71)	40 (16–70)	47 (20–67)	51 (28–71)
Females	35 (27%)	19 (31%)	13 (30%)	3 (13%)
Davies comorbidity grade				
0	103 (80%)	47 (76%)	37 (86%)	19 (83%)
1	24 (19%)	14 (23%)	6 (14%)	4 (17%)
2	1 (1%)	1 (2%)	0 (0%)	0 (0%)
Renal diagnosis:				
Glomerulonephritis	54 (42%)	25 (40%)	17 (40%)	12 (52%)
Adult polycystic kidney disease	33 (26%)	13 (21%)	13 (30%)	7 (30%)
Chronic Interstitial Nephritis	17 (13%)	10 (16%)	7 (16%)	0 (0%)
Nephrosclerosis	9 (7%)	6 (10%)	2 (5%)	1 (4%)
Other	15 (12%)	8 (13%)	4 (9%)	3 (13%)

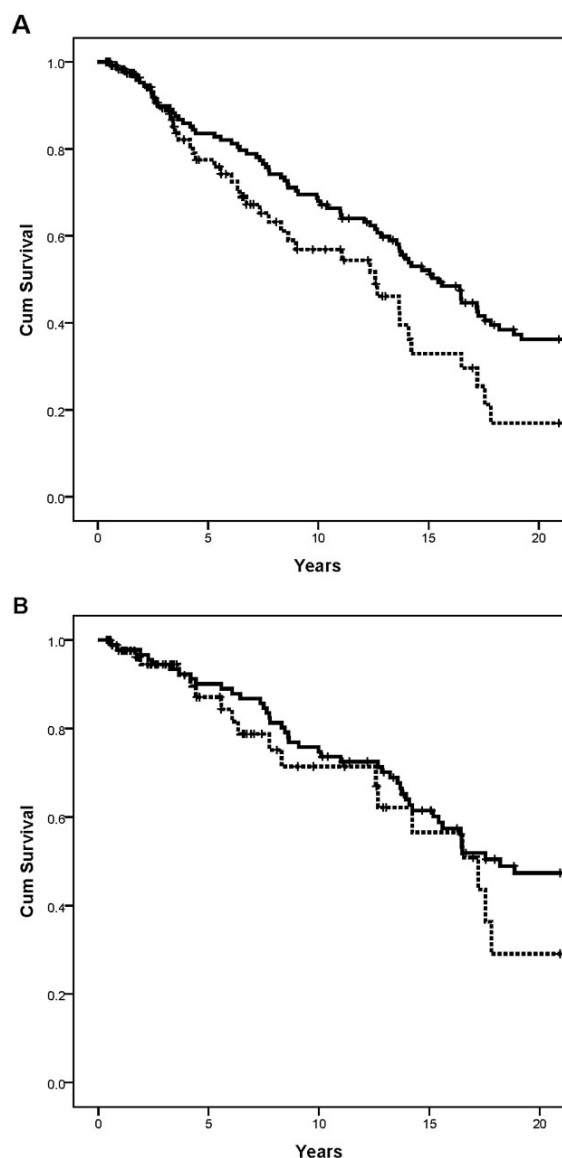


Figure 1 Long time survival of home-hemodialysis (HHD) patients and relative contribution of transplantation on survival for patients with HHD as initial therapy. In Figure 1A, survival is analyzed for all 128 incident HHD patients. In Figure 1B, survival is analyzed for a subgroup with a good prognosis (younger than 60 years and Davies index grade 0). The solid lines in the Kaplan–Meier plots represent the survival analyzed according to “intention-to-treat”. The dotted lines represent on-treatment analysis for the same patients. In the on-treatment analysis, transplantation is considered as loss to follow-up. In Figure 1B, it is shown that renal transplantation after start of HHD does not have an effect on survival for patients younger than 60 years and with no comorbidities.

Factors influencing survival

Multiple regression analysis shows that age, comorbidity and year of start of HHD were all independently related to survival ($p < 0.001$).

Age at start of HHD was a major determinant for survival as shown in Figure 2A ($p < 0.001$). For the age group < 30 years, 10-year survival was 87% compared to 38% for the age group > 60 years.

Comorbidity at start of HHD also had a major impact on survival as shown in Figure 2B ($p < 0.001$). For the 103 patients with Davies index grade 0, 10-year survival was 74%. Contrasting to this, the patients with grade 1 exhibited a 10-year survival of 46% while the one patient with grade 2 lived for 2 years after starting HHD training. The contribution of comorbidity was still significantly related to survival after adjusting for age in multiple regression analysis ($p < 0.001$). Patients without comorbidities and with an age < 60 when commencing HHD had a 10, 20 and 30-year survival of 75%, 47% and 23%, respectively.

Survival was also influenced by when patients had started HHD. In Figure 2C, patients are divided into three groups depending on the decade in which they started HHD. The survival is significantly better for patients who started HHD in each later decade ($p = 0.003$). There were no statistically significant differences in comorbidity grades ($p = 0.41$), but there was a statistically significant difference in age between these three groups of patients ($p = 0.02$). Patients who started HHD in later decades were older. The mean age for patients starting between 1971 and 1980 was 42 years and for patients starting between 1990 and 1998, 51 years. This difference in age attenuates the increase in survival over time.

There was no significant difference in survival between men and women as seen in Figure 2D ($p = 0.09$). There were no statistically significant differences in comorbidities (83% Davies grad 0 vs. 74%, $p = 0.28$) or age (46 vs. 43.0, $p = 0.36$) between male and female patients. Sex was still not significantly related to survival after adjusting for age, comorbidity and year of start of HHD ($p = 0.073$). There was no significant difference in survival between groups of patients divided according to primary renal disease.

Change in therapy and impact of renal transplantation

Many patients shifted to other modalities of renal replacement therapy (transplantation, peritoneal dialysis or in-center hemodialysis) and it was common that patients returned to HHD after a failing renal allograft (Table 2).

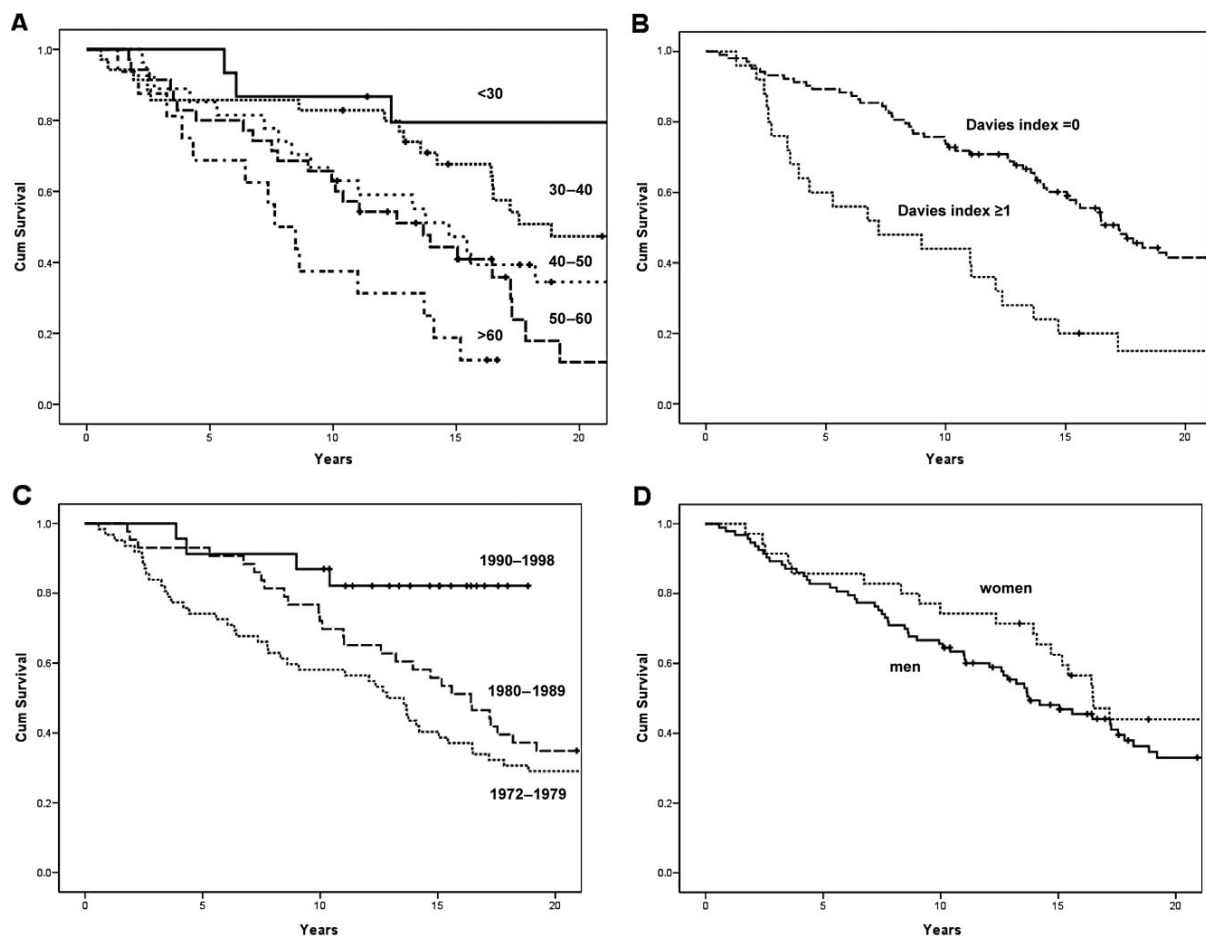


Figure 2 Factors influencing survival in home-hemodialysis (HHD) patients. A) Survival in different age groups, <30 years, 30–40 years, 40–50 years, 50–60 years or >60 years. There is a statistical difference in survival between all five age groups Log rank test, Mantel-cox $p < 0.001$. B) Survival for patients with Davies comorbidity index grade 0 or 1 and 2. Log rank test $p > 0.001$. C) Survival for patients starting HHD in 1972–1979, 1980–1989 and 1990–1998. There is a statistical difference in survival between all three decades. Log rank test, Mantel-Cox $p = 0.003$. D) Survival for male or female patients. Log rank test $p = 0.09$.

Among the 128 patients, 20 had two periods, nine had three periods and one had four periods with HHD. The median duration of the first period with HHD was 3 years (range 0.4–26). The median time spent in HHD all together was 4 (range 0.4–32) years, which corresponds to around 26% of the total time of renal replacement therapy for these patients. After 5 years, 47% of the patients who were still alive had HHD. After 20 years, most of the patients had changed renal replacement therapy, only 12% of the 33 patients still alive had HHD. The median duration of all kinds of renal replacement therapy for the patients was 14 years (range 0.6–36) (Table 3).

After starting HHD, 87 patients (68%) received a deceased or living donor renal transplant. In Figure 1A, survival on dialysis treatment is shown. By treating transplantation as “lost to follow-up” in the survival analysis, the influence of renal transplantation on survival is removed. This “on-dialysis treatment” analysis yields a 5-year survival of 78% and a 10-year survival of 57%. This is significantly shorter compared with the survival in the intention-to-treat analysis which includes influence of transplantation ($p = 0.009$). The difference between these two curves is, however, not only influenced by renal transplantation per se. Patients who received a renal transplant were younger and healthier compared with the patients

Table 2 Renal replacement therapy (RRT) 5, 10, 15, 20 and 30 years after start of home-hemodialysis

Modality of RRT	Patients n (percent of alive)				
	5 years	10 years	15 years	20 years	30 years
Renal transplantation	48 (44.9)	53 (60.9)	44 (73.3)	27 (81.8)	5 (62.5)
Home-hemodialysis	50 (46.8)	22 (25.2)	7 (11.6)	4 (12.0)	2 (25.0)
First period	40 (37.4)	16 (18.4)	3 (5.0)	1 (3.0)	0 (0)
Second period	8 (7.5)	3 (3.4)	2 (3.3)	1 (3.0)	1 (12.5)
Third period	2 (1.9)	3 (3.4)	2 (3.3)	1 (3.0)	1 (12.5)
Fourth period	0 (0)	0 (0)	0 (0)	1 (3.0)	0 (0)
Peritoneal dialysis	2 (1.9)	3 (3.4)	2 (3.3)	0 (0)	0 (0)
Institutional hemodialysis	7 (6.5)	9 (10.3)	7 (11.7)	2 (6.1)	1 (12.5)
Dead	21	41	60	77	82
Total number	128	128	120	110	90

who had not. Patients who received a renal transplant had significantly less comorbidities according to Davies index compared with patients who did not receive a renal transplant ($p = 0.004$). Mean age at start of HHD was 43 for patients who subsequently received a renal transplantation and 49 for patients who did not ($p = 0.008$). To limit this effect, a separate survival analysis was performed for the 91 patients with Davies index grade 0 and an age below 60. Seventy of these patients received a subsequent renal transplant. When limiting the analysis to these patients who started HHD with a favorable prognosis, the significant difference between the “on-dialysis treatment” and “intention-to-treat” survival curves disappeared ($p = 0.09$) (Figure 1B).

To ascertain that the small difference between the two survival analyses was not caused by poor survival among renal transplantation recipients before the cyclosporin era, separate survival curves were made for the patients with a favorable prognosis for each decade. There were no significant differences between the two Kaplan–Meier curves for the patients starting HHD in the seventies ($n = 42$,

number of deaths 37, $p = 0.33$) and the patients starting HHD in the eighties ($n = 32$, number of deaths 18, $p = 0.78$). In the nineties, there were only 18 patients younger than 60 years with Davies index grade 0 who started HHD. Among these patients, only one died, 2 years after a renal transplantation.

DISCUSSION

The long-term survival for the incident HHD patients in the present study was high, with a 10-year survival of 68% and a 20-year survival of 36%. The 10-year survival for all incident patients in SNR starting renal replacement therapy (including renal transplantation), during this period (1971–1998), was 34%.

Three other HHD studies, by Mailloux, Saner and Arkouche, have reported similar 10-year survival rates (range 63%–77%).^{5,11,16} Other studies, following patients for less than 5 years, have shown 1-year mortality between 2% and 16%.^{1–6,8–11,13,16} All the HHD studies with a 1-year mortality above 5% had included patients during the

Table 3 Duration of home-hemodialysis and all renal replacement therapy (RRT)

	Patients n	Median duration (Range) years	Mean duration (1 SD) years
Total treatment with home-hemodialysis (HHD)	128	3.6 (0.4–31.5)	5.6 (5.3)
First period of HHD	128	3.1 (0.4–26.4)	4.6 (4.4)
Second period of HHD	20	3.4 (0.3–11.5)	3.7 (2.9)
Third period of HHD	9	2.0 (0.4–16.3)	4.5 (5.1)
Fourth period of HHD	1	7.3	7.3
All RRT	128	13.9 (0.6–35.7)	15.1 (35.1)
RRT—until death	88	11.1 (0.6–31.8)	12.0 (8.0)
RRT—until December 31, 2008, living patients	40	23.0 (10.2–35.7)	21.9 (7.7)

sixties and seventies.^{1,3,4,21} We also found in the present study, that patients starting in earlier decades had significantly lower survival, despite being younger as compared to patients starting in later decades. It is unlikely that improved survival over time should be related to changes in patient selection. Improvement in treatment over time is a more likely explanation.

Indications for dialysis therapy in uremia changed considerably in Sweden during the study period. The incidence of renal replacement therapy was 16 per million in 1970²⁸ and rose to 132 per million in 1998 according to SNR. During this period, mortality in end-stage renal disease decreased.²⁸ Between 1970 and 1985, the mean age of patients accepted for dialysis increased from 31 to 63 years.²⁸ During the 30 years of inclusion to HHD in our study, indications and patient incentives for HHD also changed. The higher mean age for patients starting HHD during later decades probably reflects the aging of the general dialysis population. The increased use of peritoneal dialysis and increases of living donor transplantations probably have affected the recruitment of younger patients to HHD in the later part of our study.

How patients are selected to the HHD modality is probably a major explanatory factor for the low mortality. The patients in our study were relatively young when starting HHD, with a median age of 46 years, compared with 61 years for all patients included in SNR starting renal replacement therapy during the same period. Unfortunately, comorbidity was not registered in SNR before the nineties. Some earlier studies reporting on patient survival have not described patient populations with respect to comorbidities which makes comparison between studies difficult. However, in the study by Saner et al. the patient population was similar to the population in our study with a mean age of 50 years and 80% of the patients having low risk according to the Khan comorbidity index.¹¹ In the studies by Pauly¹⁰ and Lockridge,¹⁹ mean age at start of HHD were 46 and 52 years, but comorbidities were not reported using an index. The patients in these studies were not incident for renal replacement therapy, making comparison with our study difficult. In our study, patient selection to HHD had a significant impact on survival. Survival is significantly better for younger patients and patients with low comorbidity according to Davies index. There were no significant differences in survival between male and female patients or between different primary renal diseases in our study. However, the number of patients with diabetic nephropathy was low in the present study. Diabetes has earlier been shown to be an independent predictor of mortality for patients with HHD.²³

Home-hemodialysis as dialysis modality probably also influences survival and the impact on survival probably increases over time. In this study, HHD patients as a group received more hours of dialysis per week compared with available data from SNR about other Swedish hemodialysis patients. The mean time per week for the patients in this study 6 and 12 months after start of HHD was 17 hours. Previous studies have reported an association between longer dialysis time and improved parameters related to fluid balance²⁹ mineral metabolism²⁹ and survival.^{30,31} Moreover, the HHD patients also participated in an extensive education program during training, which probably increased their ability to understand other aspects of the treatment of CKD such as fluid balance and phosphate control. In an earlier study, patients who had participated in a predialysis education group experienced less functional disabilities, better mood and lower levels of anxiety within the first 6 months after having started dialysis, factors which might well enable patients to better understand their condition and its treatment.³² The empowerment due to patient education and increased understanding most probably leads to better adherence and compliance to pharmacological therapy. In another study, educational programs for patients with CKD could be directly related to better patient survival.³³

Survival on HHD has previously been compared with peritoneal dialysis^{5,7,9,13,17,18} and in-center hemodialysis.^{5,8,11-14,17,18} Most studies show a benefit for HHD, the only exception being a registry study from the USA.³⁴ In this study, however patients with hemodialysis in long-term facility care were registered as having HHD, emphasizing the importance of taking comorbidities into account. However, only three of the earlier studies^{11,14,18} take both age and comorbidity into account. Two of these studies,^{11,14} however, are not limited to new patients starting renal replacement therapy making comparison cumbersome as previous treatment on other dialysis modalities or renal transplantation also affects survival.

A few studies have compared survival between patients with HHD and renal transplant. Lowrie compared survival for patients starting HHD or receiving their first renal transplant during the sixties and seventies. Although patients starting HHD were older, they found no significant difference in survival compared with patients receiving a related living donor renal transplantation. Furthermore, survival was significantly better for patients starting HHD compared with patients receiving deceased donor renal transplantation.²⁰ Price showed that patients with renal transplants lived significantly longer compared with patients with HHD.²¹ The patient populations are not

described but the mortality for patients with HHD is high compared with other studies which might be explained by old age and high comorbidity risk for these HHD patients. Both these studies only include patients during the sixties and seventies, a factor we found to be associated with low survival. In the study by Pauly, with more recent data, from 1994 to 2006, there was no significant difference in survival between HHD patients and patients with renal transplants from deceased donors but there was a significantly higher survival for patients with renal transplants from living donors. Five-year survival for HHD patients was 84.5% compared with 91.3% for patients with living donor transplantation. Some of the difference might be explained by patient comorbidities and age. Patients with HHD had more peripheral vascular disease, ischemic heart disease and history of cancer. The groups were matched according to diabetes. Patients were also older compared with living donor transplant patients.¹⁰ This, once again, emphasized the importance of age and comorbidity on survival.

In the present study, no comparison of survival between patients starting HHD and other renal replacement therapies was possible as a control population was not available. However, we have attempted to estimate the impact of renal transplantation after HHD on survival. It is an important factor as 68% of the patients received a renal transplant at some point after commencing HHD. The question is to what extent does transplantation contribute to the good survival?

When all patients were included in the analysis there was a significantly better survival related to subsequent renal transplantations. The survival advantage was still much smaller compared with the survival advantage for HHD related to other modalities of dialysis in Sweden. Our interpretation is that this improved survival can be explained by the low age and comorbidity risk for patients who had received transplants. As shown in Figure 1B, for patients younger than 60 years and with no comorbidities receiving a renal transplant had no major influence on patient survival. However, our analysis has certain limitations as we do not have a separate control group of matched renal transplant patients.

In conclusion, this study shows that long-term survival on HHD is good, has improved over time and can be a good alternative to renal transplantation for certain patients. Younger age, low number of comorbidities and later decade of start of HHD all affected survival positively, while gender and renal disease had no effect. Moreover, subsequent renal transplantation was not a survival benefit in patients with an age below 60 and with no comorbidities at start of renal replacement therapy.

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Paper II



Original Paper

Home- or Institutional Hemodialysis? – a Matched Pair-Cohort Study Comparing Survival and Some Modifiable Factors Related to Survival

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Key Words

Survival • Home hemodialysis • Hypertension • Volume control • Calcium and phosphate metabolism

Abstract

Background/Aims: Survival for dialysis patients is poor. Earlier studies have shown better survival in home-hemodialysis (HHD). The aims of this study are to compare survival for matched patients with HHD and institutional hemodialysis (IHD) and to elucidate the effect on factors related to survival such as hyperphosphatemia, fluid overload and anemia. **Methods:** In this retrospective, observational study, incident patients starting HHD and IHD were matched according to sex, age, comorbidity and date of start. Survival analysis was performed both as "intention to treat" including renal transplantation and "on treatment" with censoring at the date of transplantation. Dialysis doses, laboratory parameters and prescriptions of medications were compared. **Results:** After matching, 41 pairs of patients, with HHD and IHD, were included. Survival among HHD patients was longer compared with IHD, median survival being 17.3 and 13.0 years ($p=0.016$), respectively. The "on treatment" analysis, also favoured HHD ($p=0.015$). HHD patients had lower phosphate, 1.5 mmol/L compared with 2.1 mmol/L ($p<0.001$) and no antihypertensives and diuretics compared with 2 for IHD patients at 6 ($p=0.001$) and 18 months ($p=0.014$). There were no differences in hemoglobin or albumin. **Conclusion:** HHD shows better survival compared with IHD, also after controlling for patient selection. This could be caused by better phosphate and/or fluid balance associated with higher dialysis doses.

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Introduction

Despite improvement over time, survival for patients on maintenance dialysis is still poor. According to the Swedish Renal Registry (SRR), annual mortality for patients on dialysis was 30% in 1991 and 21% in 2012 [1]. Several studies have indicated a lower mortality for patients on home hemodialysis (HHD) [2-7]. We have previously reported an annual mortality of 4.9% for patients starting HHD in Lund during 1971-1998, with decreased mortality for each decade [8].

However, patients starting HHD are younger and healthier compared with patients starting on other dialysis modalities. It is still not clear whether there is a survival advantage related to HHD beyond patient selection, and if so the magnitude of the advantage and the cause of it.

A survival advantage for HHD beyond patient selection would most probably be mediated through improvement in risk factors for death common to all dialysis patients. Important characteristics of HHD are higher dialysis doses and more extensive patient education, which both have been linked to improved survival [9-11].

In order to elucidate these issues we conducted a retrospective, observational study with matched patients starting HHD and IHD as a randomized controlled trial is not feasible. The patient populations are collected from the HHD program at Lund University Hospital and from the IHD center at Malmö General Hospital in Sweden.

The main aim of this study was to compare survival in HHD patients with control IHD patients matched for sex, age, comorbidity and start period. A secondary aim was to study the effect of HHD as compared with IHD on factors related to survival such as subsequent renal transplantation, hyperphosphatemia, hypertension, anemia and hypoalbuminemia.

Materials and Methods

Inclusion and matching criteria

Incident patients starting HHD at Lund University Hospital from January 1st 1983 to December 31st 2002 were eligible for the study if an appropriate IHD patient fulfilling the matching criteria listed below could be found among patients starting IHD at Malmö General Hospital. HHD patients were recruited from all over the Southern Health Care Region. An "incident patient" was defined as having less than 6 months with renal replacement therapy preceding start of HHD training.

Control incident IHD patients were required to have the same sex, the same level of comorbidity according to Davies Comorbidity Index [12], similar age (<5 years difference) and similar start date of IHD (<5 years difference). Davies Comorbidity Index is based on seven groups of comorbidities, malignancy, ischemic heart disease, peripheral vascular disease, left ventricular dysfunction, diabetes mellitus, systemic collagen vascular disease and other significant pathology with impact on survival in the general population. Patients with none of these comorbidities have grade 0, those with 1-2 have grade 1 and those with 3 or more comorbidities have grade 2. As only patients completing HHD training were included in the study, patients receiving IHD for less than the median training period (72 days) were not accepted as matching controls in this study.

During the inclusion period, 118 patients started HHD training in Lund. Of these, 38 were not incident and 14 patients did not complete the training. Of these 14 patients, 6 changed to IHD, 5 received a renal transplant, 1 changed to PD and two were lost to follow-up after stopping HHD training and moving to other hospitals. Adequate matching patients with IHD were found for 41 of the remaining patients (Figure 1).

IHD patients were eligible for matching if they had started dialysis between January 1st 1978 and December 31st 2007. During that period 377 patients started IHD at Malmö General Hospital. Every other HHD patient was matched with an IHD patient who had started within 5 years prior to or 5 years after the HHD patient's starting date. For each pair of patients matched according to start date and age, the remaining matching criteria were obtained from the patients' medical files.

The majority of the HHD patients had their first dialysis at the HHD training clinic but 3 patients had PD, 9 had IHD and 2 patients had an unsuccessful renal transplant just before start of HHD. Among the IHD patients only one had a short period with PD before start of IHD.

Collection of clinical data

Date at start of dialysis, (i.e. start of HHD training or IHD) and information on switches to other renal replacement therapies were collected from patient files and the SRR. Survival data were collected from the Swedish Census. All other clinical data were collected from patient files.

Data on patient characteristics were collected at start of renal replacement therapy. Other clinical data were collected from start of HHD or IHD and until 18 months after start.

Weekly dialysis duration, frequency and blood flow were recorded at 6 and 18 months after start of HHD or IHD, respectively. Data on dialysis access were registered at start of HHD or IHD and at 18 months.

A time-averaged value of the levels of phosphate, calcium, hemoglobin and albumin in plasma/serum was calculated using all analyses performed during the period 6-18 months after start of HHD or IHD. The calculations were performed using an "area under the curve" approach and the number of data points varied between 1 and 60. For patients stopping dialysis before 18 months (transplantation/death/change to another dialysis modality), only data up to the date of such an event was used for the calculations.

The number of prescribed phosphate binders was recorded according to Anatomic Therapeutic Chemical Classification, ATC-codes, according to WHO [13], at 6 and 18 months after start of HHD or IHD. Prescriptions of anti-hypertensive drugs and diuretics were recorded as Defined Daily Doses (DDD), according to WHO [14] and as number of drugs according to ATC codes at 6 and 18 months. Prescriptions of erythropoiesis stimulating agents (ESA) were recorded as DDD at 6 and 18 months.

For HHD patients, blood pressure at the visit to the clinic in closest proximity to 6 and 18 months after start of HHD was recorded. For IHD patients, mean pre-dialysis blood pressure during the 6th and 18th month after start of IHD was recorded.

All patients were followed until death or January 1st 2013. No patient was lost to follow-up.

Statistical Analysis

Statistical analyses were performed with IBM SPSS version 20 and GraphPad Prism 6.

For survival analysis Kaplan Meier curves and Breslow test were used. All patients were included in the survival analysis. Survival analysis was performed as intention to treat analysis, where patients were considered at risk also after changes to other modalities of renal replacement therapy, including transplantation. To remove the impact of differences between the groups after subsequent renal transplantation survival analysis was also performed as on treatment analysis, where patients were censored as lost to follow up on the day of renal transplantation but not when switching to another dialysis modality.

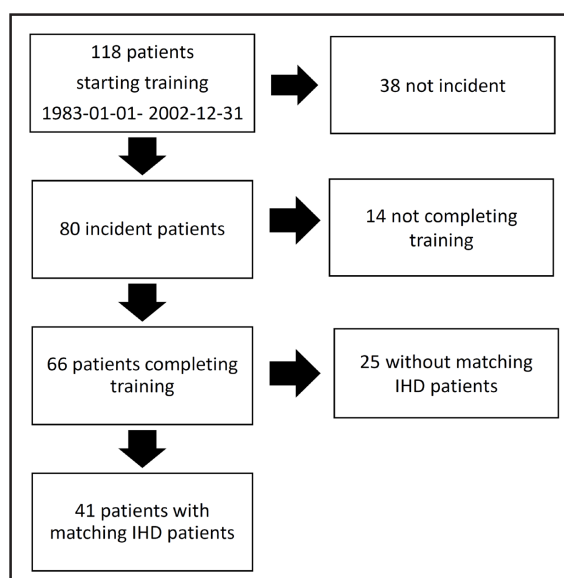


Fig. 1. Flow-chart showing selection of HHD patients. Of 118 patients starting HHD in Lund during the study period January 1st 1983 to December 31st 2002, 38 were not incident. Of the remaining patients, 14 did not complete the training. 66 patients met the inclusion criteria but for 25 of these no adequate matching IHD patient was found.

Table 1. Patient characteristics at start of renal replacement therapy and duration and frequency of renal replacement therapies

	HHD	IHD
Patients number	41	41
Median age (range) years	51.5 (19.4 -71.3)	53.9 (18.9 -74.0)
Females	10 (24 %)	10 (24 %)
Davies comorbidity grade		
• 0	29 (71 %)	29 (71 %)
• 1	12 (29 %)	12 (29 %)
• 2	0 (0 %)	0 (0 %)
Renal diagnosis		
• Glomerulonephritis	23 (56 %)	18 (44 %)
• Adult polycystic kidney disease	11 (27 %)	9 (22 %)
• Diabetes nephropathy	1 (2.4 %)	5 (12 %)
• Nefrosclerosis	1 (2.4 %)	2 (5 %)
• Other	5 (12 %)	5 (12 %)
• Unknown	0	2 (5 %)
Median duration (Range) Years		
• First period with HHD/IHD	1.8 (0.5-12.2; n=41)	1.7 (0.2-27.0; n=41)
• Total treatment with HHD	2,7 (0.5-24.9; n=41)	0 (n=0)
• Total treatment with IHD	0.6 (0.02-19.0; n=26)	1.8 (0.2-27.0; n=41)
• Renal transplantation	10.6 (0.02-28; n=33)	11.7 (0.05-27.1; n=23)
• Follow-up until January 1st 2013	14.2(4.3 -29.9; n=41)	10.8(0.21-28.4; n=41)

Only matched pairs with complete values were included in other comparisons between groups and paired tests were used. Paired t-test was used for laboratory parameters. Mc Nemar was used for dialysis access and Wilcoxon matched-pairs signed rank test was used for dialysis prescriptions and medications. Descriptive data are given as mean and standard deviation or median and range (minimum and maximum).

As blood tests are not taken with equal intervals, I e every week or month, the “area under the curve” approach was used for laboratory parameters. This is a better measure of the patients mean values compared with just the plain mean. For example values of hemoglobin taken every day when a patient has a gastrointestinal bleeding will have the same impact on the mean value as hemoglobin values taken monthly when the patient is not bleeding.

Ethics

The study was approved by the Regional Ethical Review Board in Lund.

Results

Patient characteristics and renal replacement therapies during the study

A total of 41 matched pairs of HHD and IHD patients were included in the study. Median age for included HHD and IHD patients was 51.5 and 53.9 years, respectively, and 24 % of all patients were female. Most pairs had a Davies Comorbidity Index of 0 (71 %), none had an index higher than 1. Davies Comorbidity Index grade 1 represents 1-2 comorbidities. The most common comorbidity for HHD patients was systemic collagen vascular disease (12 %), followed by diabetes mellitus (5 %). Only one of the HHD patient had 2 comorbidities, systemic collagen vascular disease and chronic obstructive lung disease. Out of the patients with IHD and Davies Comorbidity grade 1, 15 % had 2 comorbidities. Diabetes was the most common comorbidity (17%), followed by peripheral vascular disease (7 %), ischaemic heart disease (7 %) and systemic collagen disease (5 %). For both HHD and IHD patients, glomerulonephritis was the most common renal diagnosis followed by adult polycystic kidney disease (Table 1).

Median follow up duration was 14 (range 4-30) years for HHD patients and 11 (range 0.2-28) years for IHD patients. In both treatment groups a majority of patients changed renal replacement therapy after start of HHD or IHD. Only one patient in each group continued their initial treatment modality until the end of follow-up, while 2 HHD patients and 15

IHD patients died without change in therapy. At 6 months after start, no HHD patient but 7 IHD patients had switched to other dialysis modalities or received a renal transplant. At 18 months 16 HHD and 19 IHD patients had switched renal replacement therapy. Some patients had more than one period with HHD or IHD. The median duration of the first period of HHD and IHD, was 1.8 and 1.7 years, respectively (Table 1).

Survival

All patients were followed from start of renal replacement therapy until January 1st 2013. At that date 16 (39 %) HHD patients and 11 (27 %) IHD patients were still alive.

In the Kaplan Meier analysis, survival for HHD patients was significantly longer compared with IHD patients ($p=0.016$). Mean survival for HHD patients was 17.3 years compared with 13.0 for the IHD patients (median 16.7 and 11.2 years respectively). Five-year survival was 98 % for HHD patients (n at risk 41) and 71 % for IHD patients (n at risk 30) and the corresponding figures for ten-year survival was 73 % (n at risk 31) compared with 56 % (n at risk 24; Figure 2).

Renal transplantation

After starting HHD or IHD, 33 HHD and 23 IHD patients, respectively, underwent a renal transplantation. Of these, 5 HHD patients and 4 IHD patients, did get a transplant from a living donor. If treating transplantation as "lost to follow up", i.e. as censored in survival analysis, the contribution of renal transplantation to survival is removed. In such "on treatment" analysis HHD patients still exhibited a significantly longer survival ($p=0.015$). Six of the HHD patients died before censoring compared with 17 of the IHD patients. The "on-treatment" 5 years survival, that is excluding time after renal transplantation, was 91 % for HHD patients and 67 % for IHD patients. After 10 years, only 4 HHD and 7 IHD remained at risk.

Dialysis dose and dialysis access

Median weekly duration of the dialysis sessions was significantly longer for HHD compared with IHD patients, both at 6 ($p<0.001$) and 18 months after start ($p=0.001$). At 6 months the median weekly duration was 15 hours (range 10.5-38.5) for HHD patients and 12 hours (range 8-15) for IHD patients. At 18 months the median weekly duration was 15.5 hours (range 12-28) for HHD patients and 12 hours (range 8-15) for IHD patients (Table 2).

HHD patients also had a significantly higher frequency of dialysis sessions per week at 6 months ($p=0.005$), but not at 18 months ($p=0.066$). The mean blood flow at 6 months was higher for IHD compared with HHD patients ($p=0.040$), but at 18 months the difference no longer showed statistical significance ($p=0.14$) (Table 2).

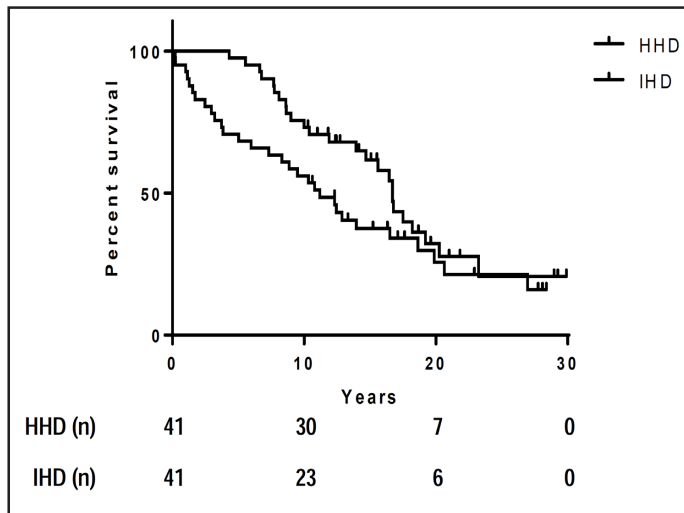


Fig. 2. Survival for matched pairs of HHD and IHD patients, respectively. Long time survival for matched pairs of home-hemodialysis patients (HHD; n=41) and institutional hemodialysis patients (IHD; n=41) ($p=0.016$ Breslow). Mean survival for HHD and IHD patients was 17.3 and 13.0 years, respectively. At ten years after start of renal replacement therapy 31 HHD patients and 24 IHD patients were still at risk. At twenty years 8 HHD patients and 7 IHD patients were at risk.

Table 2. Dialysis doses at 6 and 18 months after start of HHD and IHD

	HHD		IHD		p value		n	
Months after start	6	18	6	18	6	18	6	18
Dialysis duration per week h	15 (10.5-38.5)	15.5 (12-28)	12 (8-15)	12 (8-15)	< 0.001	0.001	28	14
Dialysis frequency per week	3 (3-6)	3 (3-4)	3 (2-3)	3 (3-3)	0.005	0.066	28	14
Blood flow ml/min	240 (200-325)	250 (200-325)	250 (225-400)	300 (250-400)	0.040	0.14	13	7

7 IHD patients had changed renal replacement therapy at 6 months after start. 16 HHD and 19 IHD patients had changed at 18 months after start. For each value only pairs of patients (n) with determinations for both patients in the pair were included in the analysis.

At start of HHD 76 % of the HHD patients had an AV fistula or graft compared with 46 % of the IHD patients ($p=0.008$). At 18 months after start of HHD or IHD (or at switch to another dialysis modality or renal transplantation before 18 months), 93% compared with 76 % patients had an AV fistula or graft ($p=0.39$).

Calcium and phosphate balance

Mean time-averaged plasma phosphate levels were significantly lower for HHD patients, 1.5 mmol/l, compared with IHD

patients, 2.1 mmol/l ($p<0.001$). There was no difference in mean plasma calcium levels between HHD and IHD patients ($p=0.33$) (Table 3). There was no difference in the number of prescribed phosphate binders according to ATC codes at 6 and 18 months, respectively, between HHD and IHD patients (21 pairs; $p=0.74$, 11 pairs; $p>0.99$). Both groups had one prescribed phosphate binder at 6 and 18 months.

Blood pressure and fluid balance

Mean blood pressure at 6 months was 141/81 mmHg for HHD patients and 151/86 for IHD patients. At 18 months mean blood pressure was 149/82 mmHg and 150/84, respectively. As recording of blood pressure was not standardized and performed under different circumstances, we did not conduct a statistical analysis.

IHD patients had a significantly higher number of antihypertensive drugs (including diuretics) based on ATC codes both at 6 ($p<0.001$) and at 18 ($p=0.014$) months after start of HHD or IHD (Table 4). At 6 and 18 months, 23 (56 %) and 16 (64 %) HHD patients, respectively, had no antihypertensive medication compared with 2 (6 %) and 1 (5 %) IHD patients.

The number of antihypertensive drugs based on ATC codes not including diuretics was significantly higher at 6 ($p=0.002$) and 18 months ($p=0.037$) for IHD patients. Based on DDD, the differences in antihypertensive drugs were not significant at 6 ($p=0.11$) or 18 months ($p=0.21$) (Table 4).

IHD patients had significantly more diuretics based on DDD at 6 ($p=0.007$) and 18 ($p=0.043$) months. For IHD patients the median DDD was 6.3 and 3.1 at 6 and 18 months, respectively. For HHD patients the median DDD was 0 at 6 and 18 months (Table 4).

Table 3. Time-averaged values of the levels of laboratory parameters 6-18 months after start of HHD or IHD

	HHD	IHD	P value (n)	n
P phosphate mmol/L	1.5 (0.26)	2.1 (0.56)	< 0.001	29
P calcium mmol/L	2.45 (0.16)	2.42 (0.16)	0.33	29
B hemoglobin g/L	106 (23)	102 (24)	0.33	29
P albumin g/L	37 (4.9)	37 (4.0)	0.56	26

Only pairs of patients (n) still on HHD or IHD at 6 months and with complete records for each value were included in the analysis. 7 IHD patients had changed renal replacement therapy at 6 months after start.

Table 4. Median number of antihypertensives and diuretics according to Anatomic Therapeutic Chemical Classification (ATC codes) and Defined Daily Doses (DDD) according to WHO at 6 and 18 months after start of HHD or IHD

	HHD		IHD		P value		n	
Months after start	6	18	6	18	6	18	6	18
Number of antihypertensives and diuretics	0 (0-3)	0 (0-3)	2 (0-5)	2 (0-5)	<0.001	0.014	26	10
Number of antihypertensives only	0 (0-2)	0 (0-3)	2 (0-4)	2 (0-4)	0.002	0.037	26	10
DDD antihypertensives	0 (0-4)	0 (0-2,4)	1,3 (0-5.2)	1,2 (0-5.67)	0.11	0.21	24	9
DDD diuretics	0 (0-13)	0 (0-13)	6.3 (0-25)	3.13 (0-25)	0.007	0.043	26	10

7 IHD patients had changed renal replacement therapy at 6 months after start. 16 HHD and 19 IHD patients had changed at 18 months after start. Only pairs of patients (n) still on HHD or IHD and with complete records for each prescription or dose were included in the analysis.

Renal anemia and plasma albumin

There were no significant differences in the time averaged blood hemoglobin concentration during the period 6 -18 months although there was a trend towards higher mean levels for the HHD patients, 106 g/L compared with 102 g/L ($p=0.33$) (Table 3). There were no significant differences in prescribed doses of ESA per week at 6 months after start of HHD or IHD (0.078). However, at 18 months the HHD patients had significantly higher doses ($p=0.038$), 7700 IE per week compared with 3010 IE per week for the IHD patients.

There was no significant difference in plasma-albumin between HHD and IHD patients ($p=0.56$) (Table 3).

Discussion

In this retrospective observational case-control study we found a significant survival advantage for HHD compared with IHD. Patients with HHD lived on average four years longer compared with IHD patients. This finding is in accordance with other retrospective observational studies, comparing dialysis at home with dialysis at an institution [4-7]. However few of the earlier studies include matching for both age, comorbidity index and start date. As randomized controlled studies are difficult and blinded studies impossible to perform in this field, well matched observational case control studies are an attractive approach for the comparison of dialysis modalities. Malmö General Hospital is located in the region of recruitment for the HHD program in Lund, but as very few patients were actually referred from Malmö to the program, IHD patients from Malmö constitute an appropriate control group.

Improved survival for patients with HHD compared with matched patients with IHD has been shown by Saner et al and by Weinhandl et al, but none of these studies have matched for both age and a validated comorbidity index [4, 7]. Other studies have taken age or comorbidity into account through multivariate analysis [4, 6, 15]. In one study, patients receiving hemodialysis at long-term care facilities such as nursing homes were defined as having HHD [15]. Albeit, that they did not perform the dialysis themselves or control dialysis dose. Multivariate analysis was used showing that survival for this form of HHD was inferior to IHD. This highlights the importance of a uniform definition of HHD versus IHD as well as that matching seems to be superior to multivariate analysis when comparing survival between dialysis modalities. Finally, in an earlier study we found that age, comorbidity index and start date of dialysis all had a major impact on survival in HHD patients [8]. Subsequent renal transplantation, has most probably contributed to survival in both groups, but was

more common in the HHD patients compared with the IHD patients in our study. By treating patients as lost to follow up after receiving a renal transplant in an “on-treatment” analysis, we can deduce that the survival advantage is not only an effect of higher frequency of renal transplantation. This is consistent with our earlier study, where we did not find a statistically significant contribution of transplantation in patients starting HHD [8]. Pauly et al has reported that survival for patients with renal transplants from deceased donors does not differ from survival in HHD patients. However, survival for patients with renal transplants from living donors was superior compared with patients on HHD [3].

The main clinical differences between the modalities are that HHD patients receive more education, are responsible for their treatment and thus accept higher dialysis doses. Devins et al has shown an association between patient education and survival for patients with chronic kidney disease [11]. The median HHD training period for the patients in Lund was 72 days and consisted of an individual but standardized educational program conducted by a specialized nurse on a one to one basis. Patients were also given freedom to increase their dialysis dose and adapt timing to their everyday lives.

The dialysis dose in this study, defined as weekly duration and frequency, was recorded at 6 and 18 months after start. Median weekly duration was longer for HHD patients compared with IHD patients both at 6 and 18 months. Interestingly, the difference in weekly duration was mainly an effect of session length. The duration and frequency, 12 hours and thrice weekly, for the IHD patients corresponds to the so-called conventional hemodialysis as described in many earlier reports studying effects of different dialysis doses [16-19]. A number of studies describe improved survival related to both prolonged session length and increased frequency of sessions [9, 10, 20]. The association between duration of sessions and mortality is shown to be unrelated to levels of Kt/V [10] indicating that factors other than the clearance of small molecules are related to mortality.

Clearance of phosphate is one such factor that differs significantly from small molecule clearance because of an aqueous cover, binding to different salts and slow transportation from the intracellular to the extracellular space [21]. Several earlier studies have shown improved plasma phosphate levels related to increased dialysis dose compared with conventional hemodialysis [16, 17, 22]. The HHD patients in our study had significantly lower plasma phosphate levels, defined as time averaged mean 6-18 months after start, compared with IHD patients. We consider 6-18 months after start to be an adequate proxy for time spent on respective dialysis modality, as well as leaving a sufficient number of patients left in treatment. Differences in plasma phosphate levels are not only related to dialysis dose, but also to dietary phosphate intake and to number and actual intake of prescribed phosphate binders. Dietary phosphate intake was not known in this study but prescription of phosphate binders was recorded. Interestingly, the number of phosphate binders according to ATC codes was the same for both treatment groups. Increased dialysis dose, increased understanding of and compliance to prescribed phosphate binders and greater adherence to dietary advice are possible explanations for the lower plasma phosphate levels in the HHD patients.

Fluid balance, blood pressure and left ventricular hypertrophy are other factors that are related to survival [23, 24] and improved by a higher dialysis dose [16, 17, 22, 25]. Some earlier studies have described associations between increased dialysis dose and decreased blood pressure and prescription of antihypertensive drugs [16, 22, 25]. In one of these studies, by Nesrallah et al, interdialytic weight gains were also studied and shown to be decreased with increased dialysis dose [25]. In our study the median number of antihypertensive drugs, with or without diuretics, was lower both at 6 and 18 months for HHD patients. The majority of HHD patients had no antihypertensive drugs or diuretics at either 6 or 18 months. Based on DDD, there were no significant differences related to antihypertensive drugs, which most probably is a reflection of the fact that DDD is defined for a population without renal failure and not applicable to patients with end-stage renal disease. The lower number of prescribed antihypertensive drugs and diuretics for HHD patients might be related to a more gentle ultrafiltration process, due to higher dialysis dose and better compliance to both prescribed

dry weight and prescribed fluid restrictions, which in turn results in less thirst and lower interdialytic weight gain.

Renal anemia is also related to survival in dialysis patients [26], but previous studies show divergent results concerning the influence of different dialysis doses [16, 17, 22]. In our study, there was a trend towards a higher hemoglobin concentration for the HHD patients. The difference might to some extent be explained by higher doses of ESA. The reason for differences in doses is not known. To our knowledge, there was no difference in target values for hemoglobin. One possible explanation is the trend that HHD patients had more frequent dialysis, which might be related to more frequent small blood losses and secondary to that higher ESA doses to maintain the hemoglobin level. It is also possible that the IHD patients received intravenous iron more frequently than the HHD patients. The average plasma levels of albumin were similar and normal in both treatment groups, thus ruling out different degrees of inflammation in the HHD and IHD patients, respectively.

Because of the retrospective design, there are limitations to this study. The most important is that despite our strict matching, there is still a risk of differences between HHD and IHD patients not controlled for. On the other hand, due to the strict matching, few patients could be included in the study. As to the factors related to survival, differences in prescriptions of phosphate binders could only be compared as number of and not as the phosphate binding index developed by Daugirdas et al [27]. Only surrogate measures, i.e. prescriptions of antihypertensive drugs and diuretics, were available, for studying fluid balance. Prescriptions of iron were missing.

Conclusion

In conclusion this study shows a significant survival advantage for HHD patients compared with IHD patients irrespective of age, comorbidity, start date and subsequent renal transplantation. HHD patients had a significantly higher dialysis dose, lower levels of plasma phosphate and were prescribed fewer antihypertensive drugs and diuretics, despite similar blood pressure, compared with IHD patients. We believe that these factors independently and together contribute to the superior survival of the HHD patients.

Disclosure Statement

The authors have no conflicts of interest.

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