PREDICTORS OF SURVIVAL ON RENAL REPLACEMENT THERAPY

Mikko Haapio

ACADEMIC DISSERTATION

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ORIGINAL PUBLICATIONS

This thesis is based on the three following publications and a submitted manuscript. In addition, it includes some unpublished data.


Study I is a joint publication; Dr. Helve has also included it among the publications of his 2014 thesis. The original publications are reproduced with permission of the copyright holders and are referred to in the text by their Roman numerals.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>APD</td>
<td>Automated peritoneal dialysis</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the receiver operating characteristics curve</td>
</tr>
<tr>
<td>CAPD</td>
<td>Continuous ambulatory peritoneal dialysis</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>ESRD</td>
<td>End-stage renal disease</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>HD</td>
<td>Hemodialysis</td>
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<td>HDF</td>
<td>Hemodiafiltration</td>
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<td>MDRD</td>
<td>Modification of Diet in Renal Disease</td>
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<td>IQR</td>
<td>Interquartile range</td>
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<td>PD</td>
<td>Peritoneal dialysis</td>
</tr>
<tr>
<td>pmp</td>
<td>Per million population</td>
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<tr>
<td>RR</td>
<td>Relative risk</td>
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<tr>
<td>RRT</td>
<td>Renal replacement therapy</td>
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ABSTRACT

Background and aims
Patients with end-stage renal disease and on chronic renal replacement therapy are at increased risk of death compared to a population of the same age without end-stage renal disease. Despite some improvement in prognosis of end-stage renal disease patients during recent decades, the expected outcome remains dismal. Several factors are associated with impaired survival of patients with end-stage renal disease: especially high age, low serum albumin, chronic inflammation, and comorbidities such as diabetes and heart failure. However, a major portion of factors behind impaired survival have been insufficiently identified, and their prognostic weight is largely unknown. We therefore targeted for further exploration and measurement of factors potentially associated with survival of patients on chronic renal replacement therapy.

Study patients and methods
In the four studies of this thesis, we investigated the survival of cohorts of adult patients in Finland after the start of chronic renal replacement therapy. These cohorts were in Study I, 1,604 patients with type 1 diabetes and 1,556 with glomerulonephritis who started chronic RRT during 1980–2005; in Study II, 319 patients during one year (1998) preceding start of chronic renal replacement therapy and thereafter; in Study III, all 4,463 patients who started chronic renal replacement therapy in 2000–2009; in Study IV, all 6,103 patients who entered chronic dialysis in 2000–2012.

Data on patient cohorts came from the Finnish Registry for Kidney Diseases, a database including comprehensive information on Finnish patients on chronic renal replacement therapy since 1964. In Study III, data also came from the Finnish Kidney Transplant Registry.

The statistical methods mainly employed in our survival analyses were Kaplan-Meier curves, the log rank test, and Cox proportional hazards regression and binary logistic regression for multivariable modeling.

Results
In Study I, we showed that survival of patients with type 1 diabetes receiving chronic renal replacement therapy has improved significantly and consistently over the years and in all age-groups. Patients entering chronic renal replacement therapy in 2000–2005 had a 77% lower risk of death than those entering in 1980–1984. Said another way, median survival time of patients with type 1 diabetes on chronic renal replacement therapy has increased from 3.6 years to more than eight.
In Study II, we detected a significantly higher age-adjusted mortality in those on chronic renal replacement therapy whose decline in estimated glomerular filtration rate during the predialysis phase had been the fastest. Their mortality risk was 73% higher in the patient tertile of fastest decliners compared to the slowest. This association, however, proved not to be causal, but instead jointly caused by many confounding factors, especially age, end-stage renal disease diagnoses type 1 diabetes and amyloidosis, and the comorbidities myocardial infarction and cancer.

In Study III, results of our primary adjusted analyses (intention-to-treat) indicated no significant difference in risk of death between patients on chronic renal replacement therapy who started with peritoneal dialysis compared to those who started with hemodialysis. Without adjustment, the relative risk of death of peritoneal dialysis patients was 0.65 (95% CI 0.58-0.73, p<0.001) compared to hemodialysis patients. With adjustment for 26 potentially confounding variables, the corresponding relative risk was, however, 1.07 (95% CI 0.94-1.22, p=0.33). Results from our secondary analysis method (as-treated) and further with full adjustment, however, indicated a 17 to 33% higher relative risk of death for patients exclusively treated by peritoneal dialysis compared to those treated by hemodialysis exclusively.

In Study IV, we developed one- and two-year all-cause mortality prediction models for patients starting chronic dialysis. These models were based on a less-recent training cohort and validated with a more recent validation cohort. As a result, area under the curve for the one-year model (with seven variables) reached 0.77 and for the two-year model (with six variables) 0.74. Because mortality in the more recent patient cohort was significantly lower than in the less-recent cohort, both models slightly overestimated mortality risk.

**Conclusions**

Based on studies described in this thesis, survival of Finnish patients with type 1 diabetes and end-stage renal disease has significantly improved since the beginning of the 1980s, despite their conspicuous increase in age, and has improved relatively more in patients with type 1 diabetes than in patients with glomerulonephritis, suggesting progress both in dialysis therapy and overall management of patients with end-stage renal disease and, quite evidently, also in management of diabetes. Furthermore, factors behind the rapid decline in estimated glomerular filtration rate during the year preceding the start of chronic renal replacement therapy, and effects of these factors on subsequent survival are now better characterized. Rate of decline in estimated glomerular filtration rate is not a causal factor for survival, but instead a marker of other factors associated with end-stage renal disease patients’ survival. In addition, based on this research, no overall difference appeared in survival regarding modality of dialysis. Patients starting chronic dialysis differ significantly between dialysis modalities with respect to many
patient-level prognostic factors, but after comprehensive adjustment for these putative confounders, no survival advantage of one dialysis modality over another emerged. And lastly, important factors affecting one- and two-year mortality of Finnish patients starting chronic dialysis are now identified and their prognostic weight can be investigated. Based on these findings, we constructed two models for survival estimation hopefully to be implemented in individualized treatment-planning of patients approaching chronic renal replacement therapy.
ABSTRACT IN FINNISH

Tutkimuksen taustaa ja tavoitteet


Tutkimuspotilaat ja –menetelmät


Tärkeimmät käytämämme tilastolliset menetelmät olivat Kaplanin-Meierin menetelmä, log rank -testi ja Coxin suhteellisten riskitiheyksien regressio sekä monen selittäjän binaarinen logistinen regressio.

Tulokset

Osatyössä I osoitimme, että tyypin 1 diabetesta sairastavien, pitkäaikaisessa munuaisten korvaushoidossa olevien potilaiden eloonjäämisennuste on parantunut merkitsevästi viimeisten vuosikymmenien aikana. Ennustetaan parantunut kaikissa ikäryhmissä. Vuosina 2000–2005 pitkäaikaiseen munuaisten korvaushoidoon tulleiden kuolemanriski oli 77% pienempi kuin vuosina 1980–1984 hoidon aloit-
Osatyössä II totesimme, että ikäväkioitu kuolemanriski oli merkitsevästi suurempi niillä pitkäaikaisessa munuaisten korvaushoidossa olevilla potilailla, joiden laskennallinen munuaiskärsääsdoksen laskuneopes dialyysia edeltävässä ns. predialyysivaiheessa oli ollut nopein. Kuolemanriski oli 73% suurempi, kun verrattiin laskennallisen munuaiskärsääsdoksen laskun osalta nopeinta potilaskolmannesta hitaimpaan kolmannekeen. Kyseessä ei kuitenkaan ollut syy-seuraussuhde munuaiskärsääsdoksen laskunepeuden ja kuolemanriskin välillä, vaan kuolemanriskin erilaisuus johtui useasta sekoittavasta tekijästä, kuten ikä, munuaisten vajaatoiminnan aiheuttanut sairaus (tyypin I diabetes ja amyloidoosi) ja sellaiset liitännäissairaudet kuten sydäninfarkti ja syöpä.

Osatyössä III verrattiin kuolemanriskiä pitkäaikaisen vatsakalvodialyysin ja hemodialyysin aloittaneiden potilaiden välillä. Vakioduussa pääanalyysissä (intention-to-treat) ei ilmennyt eroa kuolemanriskissä. Ilman vakoointia vatsakalvodialyysin aloittaneiden suhteellinen kuolemanriski oli 0,65 (95% CI 0,58-0,73, p<0,001) verrattuna hemodialyysin aloittaneisiin. Kun kuolemanriski vakoitettiin 26:lla mahdollisella sekoittavalla tekijällä, niin vastaava suhteellinen kuolemanriski oli 1,07 (95 CI 0,94-1,22, p=0,33). Toissijaisena käytämämme, täysinvakioitu analyysitapa (as-treated) osoitti 17-33% korkeampakuolemanriskiä yksinomaan vatsakalvodialyysissä olleilla potilailla verrattuna pelkästään hemodialyssillä hoidettuihin potilasiin.

Osatyössä IV kehitimme yksi- ja kaksivuotiskuolemanriskiä ennustavat mallit. Mallien rakentaminen suoritettiin pitkäaikaisen munuaisten korvaushoidon vuosina 2000–2008 aloittaneiden potilaiden tietojen pohjalta, ja mallit validoitiin (vahvistettiin) uudemmalla potilasryhmällä (vuosina 2009–2012 hoidon aloittaneet). Mallien kyky ennustaa yksilöllistä kuolemanriskiä (area under the curve, AUC) oli yksivuotismallilla (seitsemän muuttujaa) 0,77 ja kaksivuotismallilla (kuusi muuttujaa) 0,74. Molemmat mallit yliarvioivat kuolemanriskiä johtuen validointiryhmän merkitsevästi vähäisemmästä kuolleisuudesta verrattuna pelkästään hemodialyssillä hoidettuihin potilasiin.

Päätelmät

Tämän väitöskirjatyön osatöiden perusteella voidaan sanoa seuraavaa: 1) Tyypin I diabetesta sairastavien suomalaisen, pitkäaikaisessa munuaisten korvaushoidossa olevien potilaiden eloonjääminen on parantunut merkitsevästi vuodesta 1980 lähtien. Eloonjäämisennuste on laajentunut tyypin I diabetes ja amyloidoosi

Päättelmät

Tämän väitöskirjatyön osatöiden perusteella voidaan sanoa seuraavaa: 1) Tyypin 1 diabetesta sairastavien suomalaisen, pitkäaikaisessa munuaisten korvaushoidossa olevien potilaiden eloonjääminen on parantunut merkitsevästi vuodesta 1980 lähtien. Eloonjäämisennuste on parantunut siitäkin huolimatta, että munuaisten korvaushoidon aloittavan potilaat ovat vuosi vuodelta ikäämmät. Ennuste on kohentunut tyypin 1 diabetesja suhteellisesti enemmän kuin munuaiskärsääsdoksendistrict testaavat potilailla viitaten kehyksen sekä munuaisten korvaushoidojen tekniikoissa ja pitkäaikaisessa korvaushoidossa olevien
hoidossa ylipääätään, että varsin selvästi myös kehitykseen diabeteksen hoidossa.
1 INTRODUCTION

The number of patients with severe renal insufficiency and also the number on chronic renal replacement therapy (RRT) is increasing (1-3). In Finland, this is mainly due to the general ageing of the population, a high incidence of type 1 diabetes, and a growing incidence of type 2 diabetes (1). As the population with severe renal insufficiency is expanding, and especially as patients on chronic RRT live longer, the number of patients remaining on programs for chronic RRT is increasing (1).

End-stage renal disease (ESRD) raises mortality risk many-fold compared to those without ESRD (4, 5). The risk is further heightened with increasing age (6) and in the presence of comorbidities such as heart failure (7-9) and comorbid conditions such as hypoalbuminemia (10). Certain causes of ESRD such as type 2 diabetes are also associated with impaired survival (11). Of all patients starting chronic dialysis, approximately 71% are alive after two years but only 48% after five years (12). Although survival of some patient groups on RRT has improved, in general the outcome of patients on chronic RRT is dismal (13, 14). Furthermore, in addition to diabetes, other comorbidities have become more frequent among ESRD patients (7). Nevertheless, progress taken place in many areas of nephrological care (such as diabetic nephropathy), and RRT techniques (like dialysis dose and delivery), have already translated in many ESRD populations into improved prognosis (1, 15, 16).

The growing number of patients with ESRD also create growing demands on nephrological health care, not to mention the increased individual morbidity and mortality burden upon these patients (17, 18). To tackle these major obstacles, researchers have attempted to clarify factors associated with increased mortality of ESRD patients. Identifying these factors linked to poor outcome could be helpful in many ways: in 1) improving ESRD management, 2) targeting more sound use of nephrological health care resources, and most importantly 3) improving ESRD patients’ survival and quality of life.

An important and large ESRD patient group in Finland is the one with type 1 diabetes (1). Risk of patients with type 1 diabetes to develop ESRD decreased during recent past decades (19). Furthermore, according to some studies, the mortality of patients with type 1 diabetes on chronic RRT also seems to have decreased (20-22). Overall, however, data on prognosis have been very limited.

The decision on when to start chronic RRT is in most cases set individually and based on information including patient’s uremic symptoms, laboratory test results (level of renal insufficiency), and availability of RRT resources (23, 24). During the predialysis phase (i.e., time-period before start of chronic RRT) patients
with chronic kidney disease (CKD) are regularly monitored for uremic symptoms and kidney function. A common method to assess level of renal insufficiency is estimation of glomerular filtration rate (GFR) (25). The pace at which renal function deteriorates is individual: some are followed by nephrologists for years with only gradually decreasing estimated GFR (eGFR) before entering chronic RRT, while some others present with quickly worsening renal function and thus quicker RRT initiation. Many investigators have tried to discover the optimal level of eGFR at start of chronic RRT with regard to subsequent mortality on RRT, resulting in opposite estimations with respect to general expectations (26-34). However, no earlier published data exist on the association between predialysis phase change in eGFR and subsequent survival on chronic RRT.

When the start of chronic RRT approaches, the decision needs to be: which dialysis modality (i.e., hemodialysis, HD or peritoneal dialysis, PD) will be started. And further, which modality would be the most suitable for that individual patient (17, 35-37), and, would the dialysis modalities differ with respect to mortality? Several studies have focused on association of dialysis modality with survival on chronic RRT (38-56). Results have been either conflicting or showing no superiority of one modality over another. No Finnish data in the field have existed before our findings.

In addition to these factors related to outcome, many other co-existing factors are associated with survival of chronic RRT patients (6, 7, 10, 57-61). Their identification and knowing their prognostic weight would enable us to build models for individual risk-assessment (62-70), to help 1) teach nephrologists ESRD management and individualized treatment-planning, 2) give patients insight into decisions concerning their treatment, and 3) the nephrological health care system as a whole in delivering limited resources fairly and equally.
2 REVIEW OF THE LITERATURE

2.1 END-STAGE RENAL DISEASE

ESRD is the term for a situation in which renal clearance of uremic toxins has fallen to be so low that the sequel, irreversible severe renal insufficiency with uremic symptoms (fatigue, nausea, body fluid retention, pruritus, etc.), warrants chronic RRT.

2.1.1 INCIDENCE, PREVALENCE, ETIOLOGY

Between countries and populations, the incidence of ESRD (defined as start of chronic RRT) varies greatly. In 2012 the incidence was the highest in the world in Taiwan and in Jalisco (Mexico), with 467 and 450 new patients entering chronic RRT per million population (pmp) (71). In contrast, the number of ESRD patients in some European countries is among the lowest in the world, approximately 110 to 140 pmp per year in the majority of them, and approximately 130 pmp in the whole of Europe in 2013 (2). In Finland, where ESRD incidence is the lowest among the Nordic countries, an increase occurred for decades to approximately 500 (ca. 100 pmp) new patients annually. This may have resulted from the growing number with prior hypertension or type 2 diabetes, and of elderly patients accepted for active treatment programs (1). Recently, however, growth in incidence has diminished in Finland, especially among the elderly, reaching a plateau in 2004, after which there have been about 450 new cases of ESRD annually (72). In 2013, 485 new patients entered chronic RRT (89 pmp) in Finland, with approximately two-thirds of them males (1). Because the Finnish population is aging rapidly, ESRD incidence is expected to rise again in the coming years (15).

As to the prevalence of ESRD (defined as chronic RRT), it also varies significantly between populations, from Taiwan’s about 2,900 prevalent ESRD patients pmp (71), and Europe’s (as a whole) corresponding figure of 950 pmp (2), to Finland’s internationally low figure of about 800 pmp (1). By the end of 2013 in Finland, ESRD prevalence was 24% higher than in 2003 and 7% higher than in 2008 (1). The prevalence of chronic RRT patients is increasing in most countries because the number of patients entering chronic RRT exceeds that of patients leaving chronic RRT. Several factors relate to this: 1) in many countries, an increasing number of patients with severe renal insufficiency are offered chronic RRT; 2) patients on chronic dialysis live longer on dialysis; 3) the number of patients receiving a kidney transplant is increasing; and 4) the prognosis of patients with a kidney transplant is improving (1, 2, 72-74). In Finland in 2013, the number
of patient-years on chronic RRT was 4,464, of which 2,652 (59%) in patients with a functioning kidney transplant, 1,464 (33%) in patients on HD, and 348 (8%) in patients on PD (1).

Typical diseases causing ESRD have included type 1 and 2 diabetes, glomerulonephritis, nephrosclerosis, polycystic kidney disease, pyelonephritis, and amyloidosis. In 2013 in Finland, based on patient-years on chronic RRT, 16% had type 1 diabetes as the cause of ESRD, 10% type 2 diabetes, 22% glomerulonephritis, 4% nephrosclerosis, 14% polycystic kidney disease, and 6% pyelonephritis (1). The number with type 2 diabetes entering chronic RRT grew substantially until 2002 and has then stabilized. The number of patients with glomerulonephritis or polycystic kidney disease has been stable even longer, and ESRD prevalence caused by amyloidosis has significantly decreased.

2.1.2 GLOMERULAR FILTRATION RATE

The term GFR describes the volume of plasma filtrated through the renal glomeruli per unit of time. Some molecules are freely filtered through the kidneys, but for most molecules, the filtration coefficient is less than one (75). The unit used is ml/min or ml/s per 1.73 m² body surface, and, excluding possible renal reabsorption and tubular excretion, it approximates the clearance of the molecule from plasma by the kidneys. In clinical practice, the estimation of clearance of creatinine is the most commonly used method to assess a patient’s renal “purification” capability and therefore to detect possible renal insufficiency.

2.1.2.1 Estimation

The gold standard for measuring GFR is measurement of clearance of Cr-EDTA (chrome-ethylenediaminetetraacetic acid). This chrome-labeled isotope is given intravenously and, subsequently, during the following five hours repeatedly measured from blood (76). The test is laborious and expensive, and for the patient rather troublesome. Thus, for practical purposes GFR is usually calculated with mathematical formulas approximating the value of true GFR, by producing estimated GFR (eGFR). For creatinine clearance, several formulas exist: for instance, the Cockcroft-Gault formula, the various forms of MDRD (Modification for Diet in Renal Disease) formulas, and the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula (25, 77-79). They differ in possessing somewhat different measurement accuracy depending on degree of renal insufficiency (25, 79, 80).

In the studies included here, choice of the MDRD formula was based on its better measurement capability (reliability) in severe renal insufficiency compared to that of the older Cockcroft-Gault equation (77). For this reason, we favored the MDRD formula in the follow-up especially of predialysis patients (77, 81). Of
note, the newer CKD-EPI formula, presently used was not yet widely used when these studies were performed. The MDRD formula used herein was:

\[
\text{eGFR (MDRD)} = 175 \times (\text{plasma creatinine in } \mu\text{mol/L}/88.4)^{-1.154} \times \text{age}^{-0.203} \text{ for males. Equation is multiplied by 0.742 for females (77).}
\]

CKD is staged depending on degree of chronic renal insufficiency (Table 1) (82).

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>Degree of renal insufficiency</th>
<th>GFR, ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>&gt;90</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>60-89</td>
</tr>
<tr>
<td>3A</td>
<td>Moderate</td>
<td>45-59</td>
</tr>
<tr>
<td>3B</td>
<td></td>
<td>30-44</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>ESRD</td>
<td>&lt;15 or on dialysis</td>
</tr>
</tbody>
</table>

All GFR values are normalized to an average surface area (size) of 1.73 m²

2.1.2.2 Factors associated with rapid eGFR decline

Investigators have found factors associated with rapid deterioration of renal function, even to the stage of ESRD (83, 84). Decline in eGFR is especially rapid in acute severe nephrological diseases, including rapidly progressing glomerulonephritis and vasculitis, and acute kidney injury in certain poisonings (85-87). Often this is the case also in patients with acute kidney injury imposed on pre-existing chronic renal insufficiency (88). In a more chronic setting, the diseases causing ESRD vary in their typical eGFR decline pattern; for instance, patients with type 2 diabetes usually have a more rapid decline than do patients with primary renal disorders such as polycystic disease or pyelonephritis (89, 90). Some other non-specific, comorbid characteristics are associated with accelerated rate of eGFR decline. Albuminuria, hematuria, high age, male gender, low serum albumin, high serum phosphate, metabolic acidosis, hyperlipidemia, anemia, certain comorbidities (hypertension, left ventricular hypertrophy) and late nephrology referral have been associated with enhanced CKD progression during the predialysis phase (84, 91-93). Identification of risk factors for progression of CKD to ESRD could provide potential targets for preventive interventions (83, 94). However, despite efforts to discover factors affecting the rate at which renal function declines, progressing to ESRD, our knowledge of rapid eGFR decline is limited.
2.1.2.3 Pattern of eGFR decline and mortality

At the time of starting maintenance (chronic) RRT, patients present with stage 5 CKD (eGFR < 15 ml/min/1.73 m²). The patterns and speeds at which patients enter chronic RRT, however, differ greatly. In the acute setting, the approach is often rapid and may last only from days to weeks, whereas patients with gradually worsening chronic renal insufficiency often approach chronic RRT with rather steadily declining eGFR and over a period of up to several years (91).

The pace at which eGFR declines and its subsequent effect on mortality has been the topic of several investigations (95-98). Rifkin and colleagues investigated creatinine and serum cystatin C in an elderly cohort of 4,380 patients with mild renal insufficiency (i.e., not yet with predialysis phase insufficiency), in which a yearly eGFR decline over 3 ml/min/1.73 m² was associated with an increased risk for cardiovascular and all-cause mortality (95). Wu and colleagues followed 573 CKD 3-5 patients for 12 months to investigate the effect of multidisciplinary predialysis patient education on risk for developing ESRD or dying, and found that the patients who had received enhanced training had a slower eGFR decline and, furthermore, were at decreased risk of death during the predialysis phase and had a decreased need to enter chronic RRT (96). Survival on chronic RRT was not analyzed.

In a more recent study, Chen and colleagues found that predialysis patients with early nephrological referral (over six months before start of chronic RRT) showed better survival than did those patients with later referral (97). Survival in this cohort was analyzed from an estimated time-point at which eGFR was below 15 ml/min/1.73 m². In all these studies, survival was analyzed for patients with varying CKD stages, with none of the studies extending to assess mortality after chronic RRT start. Importantly, no prior studies report specifically the effect of pace of eGFR decline during the predialysis phase on subsequent survival when on chronic RRT.

2.1.2.4 eGFR at RRT start and mortality

Knowledge of predialysis factors affecting outcome on RRT is limited; the same can be said about our knowledge of the optimal timing of start of chronic RRT with regard to survival when on chronic RRT. It was generally believed that early RRT start (i.e., at higher eGFR) is important for patients’ well-being and connected to better outcome (99, 100). This was based on observational or retrospective studies with potential bias related to patient selection, laboratory methods, or lead-time in dialysis initiation (99, 101). The opposite emerged later, when many observational studies paradoxically showed that survival of patients starting RRT at lower eGFR values was better than (29, 102) or no different (103) from that of starters with higher eGFR. However, in the only randomized controlled trial comparing early to late dialysis start, no survival difference appeared (104). In
that trial, patients were randomly assigned to 1) start dialysis when eGFR was 10-14 ml/min/1.73 m² (early-start group, n=404) or 2) to continue with routine care until eGFR reached 5-7 ml/min/1.73 m², at which point dialysis was started (late-start group, n=424). During the follow-up (median 3.6 years) 152 patients in the early-start group and 155 patients in the late-start group died, with no significant difference in survival (hazard ratio for death in the early-start group 1.04; 95% confidence interval, 0.83-1.30, p=0.75). Of note, however, the true difference between the study groups in mean eGFR (MDRD) value at RRT start was rather small (9.0 versus 7.2 ml/min/1.73 m²), and as many as 76% of the patients in the late-start group started RRT with eGFR over 7 ml/min/1.73 m².

2.2 CHRONIC RENAL REPLACEMENT THERAPY

Chronic RRT is started when a patient presents with ESRD, and renal clearance of uremic toxins has diminished to a level causing uremic symptoms, which usually happens when GFR decreases to less than 10 ml/min/1.73 m² (100). The start of chronic RRT is usually preceded by a so-called predialysis phase, during which the patient is closely and regularly monitored by a nephrological unit to give individualized treatment for uremia and to detect and respond to findings (symptoms, laboratory test results) necessitating start of RRT (100).

2.2.1 MODALITIES

The three main modalities of chronic RRT are HD, PD, and kidney transplantation (105). The two main forms of dialysis, HD and PD, are technically unique and different from each other, and both include several subforms. In the third chronic RRT modality, kidney transplantation, a functioning kidney is transplanted.

2.2.1.1 Hemodialysis

HD is a RRT technique in which a patient’s blood is directed through a specific filter (hemodialyzer, hemofilter) containing very small, hollow-fiber capillaries (106). The membrane walls of the capillaries contain microscopically small pores making the capillaries semipermeable and thus capable of allowing some (especially; small) molecules to pass from the blood circulation to the outside of the capillaries and into the dialysis fluid. The dialysis fluid flows in the hemodialyzer, outside of the capillaries and in the opposite direction to that of the blood. Access to a patient’s blood is obtained via 1) a two-lumen catheter inserted into a central vein enabling blood to be both drawn in and returned simultaneously, or 2) via an arteriovenous fistula or an artificial arteriovenous graft in which two dialysis needles are placed. If there is no pressure gradient between the blood and dialysis fluid, the technique
uses pure diffusion (osmosis) to transport the molecules of higher concentration in the blood to the lower concentration in dialysis fluid (106). HD is especially effective for removing small (molecular weight < 500 Dalton), water-soluble, non-protein-bound uremic toxins (e.g., urea, potassium, phosphorus) from the blood, and depending on dialyzer and the size of its capillary pores, this technique is variably effective also for removing molecules of larger molecular weight (e.g., beta-2-microglobulin, immunoglobulin light chain, molecular weight 500 to 60,000 Dalton). The effectiveness of toxin clearance by the dialyzer also depends on the area of its capillaries’ surface, and, on rates of blood and dialysis fluid flow.

When a pressure gradient is applied to the dialyzer, and no dialysis fluid is used, the technique used is called convection (107). With this technique (isolated ultrafiltration), plasma water may be removed from a patient, aiming at diminishing fluid overload. However, along with removed plasma water, small, clinically non-relevant amounts of uremic toxins also shift from the blood to dialysis fluid, but only at a concentration in which they are diluted in the blood, and thus this technique does not effectively clean a patient’s blood of uremic toxins. Diffusion and convection techniques can also be combined, in which case simultaneous HD is done at the same time with removing excess fluid from a patient (108).

Hemofiltration implies a technique in which the amount of ultrafiltration exceeds the amount of fluid removal desired for a patient, and thus replacement fluid (also called filtration fluid) must be infused into a patient’s blood to maintain hemodynamic stability and targeted fluid balance (109). The replacement fluid is infused either before or after the hemodialyzer (pre- or postdilution), with simultaneous removal of at least the same amount of fluid in the dialyzer. This technique mainly uses convection, but also exerts its clearance with diluting and correcting concentration of uremic toxins in the blood by the specific content of the filtration fluid. For instance, if potassium concentration in the blood is 6 mmol/L, and the concentration in the filtration fluid is 2 mmol/L, the blood concentration of potassium is inevitably and gradually reduced by the infusion of filtration fluid. Consequently, when removing a corresponding amount of the diluted plasma water in the dialyzer, uremic toxins may be purified from a patient. The clearance of toxins by hemofiltration depends mostly on the rate of filtration fluid infused and removed (109).

When diffusion and convection techniques are combined, the technique is called hemodiafiltration (HDF), with enhanced clearance of solutes in a wide spectrum of molecular weights compared to purely diffusive HD (108, 110). There are several forms of HDF modality, including high-volume HDF and online HDF, with either pre- or postdilution infusion of filtration fluid (110). HDF is a newer technique than HD, and its use is gradually increasing along improvements accomplished in dialyzer development and technology allowing
use of large amounts of ultrapure online filtration and dialysis fluids. HDF offers higher clearance of uremic toxins than HD, and there are data suggesting increased survival in patients treated with online HDF (50, 108). With the additive clearance effect of filtration fluid (aka., replacement fluid) used in HDF, the clearance is further increased by the so-called high-flux dialyzers, with a highly permeable membrane and larger membrane area compared to low-flux dialyzers, which are still the mainstream in HD (106). Another advantage of HDF is associated with the better hemodynamic tolerance it carries for some patients (108, 111). This effect, however, is probably mainly caused by enhanced cooling of blood in HDF compared to standard HD (108, 112). In Finland, about 21% of all chronic HD patients receive HDF (74).

2.2.1.2 Peritoneal dialysis

PD is a RRT modality in which removal of uremic waste products takes place by diffusion in the peritoneal cavity, across the peritoneal membrane from the underlying capillaries into PD fluid (113). Excess plasma water passes into PD fluid caused by the relative hyperosmolality of PD fluid. The PD fluid (also called dialysate) is infused into a patient’s peritoneal cavity through a permanent silicon rubber tube (PD catheter), which is inserted either laparoscopically or with open (surgical) placement and extends from the cutaneous surface and through the abdominal muscles to lower parts of peritoneal cavity (114). After an individually suitable dwelling time (usually a few hours), during which uremic toxins and fluid are transported into PD fluid, the fluid (i.e., dwell) is drained out of the peritoneal cavity through the same one-lumen PD catheter. After that, fresh fluid is again infused into the peritoneal cavity for about 10 to 15 minutes’ time, and a new cycle of PD treatment is started. PD fluid typically consists of, in addition to sodium, chloride and bicarbonate, a high percentage of glucose to create hyperosmolality, which is responsible for the ability of PD fluid to remove excess plasma water from the blood circulation (115). Usually the total volume of infused PD fluid used at one time is 1500 to 2500 mL. The volume of outflow fluid depends on how much extra removed fluid accompanies the dialysate, and how much of the dialysate is absorbed (116).

There are several forms of PD. Internationally the most popular one is continuous ambulatory PD (CAPD) (2), in which fresh PD fluid is infused approximately every four to six hours, and typically four to five times a day (usually with a longer dwelling time during the night) (114). CAPD is, however, a rather laborious and time-consuming technique which usually requires the patient to be at home at regular times of drainage and infusion of new fluid. Due to this, automated PD (APD) has gained increasing popularity, allowing treatment-free day-time while a PD machine performs the fluid exchanges during the night with the patient asleep (117, 118). The drawback of APD compared to CAPD is,
however, its considerably higher cost. Overall, most forms of PD treatment can be considered advantageous over in-center HD in that they can be performed at home and thus without the patient needing often to visit a nephrological unit (119).

On PD, clearance of uremic toxins mainly depends on the intensity of PD treatment and characteristics of the peritoneum (113). In general, depending on the individual’s particular peritoneal characteristics, PD is intensified by either an increase in number of fluid exchanges or an increase in dwelling time, and by use of PD fluids containing higher concentrations of glucose. Characteristics of the peritoneum between individual patients vary greatly; whereas the transport of toxins and exchange of fluids in some patients occur rapidly, in some others it takes longer, and patients’ peritoneal characteristics must be taken into account in individualized management of PD (113).

2.2.1.3 Kidney transplantation

In kidney transplantation, a functioning kidney is transplanted either from a deceased or a living donor. The transplant is placed underneath the abdominal skin and muscles in the extraperitoneal space, on the anterior side of the abdomen, either right or left. Depending on many factors, the transplant may already start functioning during the operation or soon after the transplantation, or it may exhibit delayed graft function, and sometimes, although fortunately not often, will never function. As both recipients and donors have become older during recent years, the incidence of delayed graft function has increased (failure of serum creatinine level to decrease by 10% on three consecutive days during the first postoperative week) (120). Already approximately 50% of the recipients experience late onset for the graft to function (121).

Of all chronic RRT modalities, kidney transplantation can be considered the one best resembling and replacing the earlier native kidney which ceased to function, and therefore also the most physiological modality of chronic RRTs (122). Although immunosuppressant therapy and many other medications are mandatory after transplantation, the use of, for instance, erythropoiesis-stimulating agents, phosphate-lowering agents, and agents for treating secondary hyperparathyroidism may in many cases be significantly reduced or even discontinued (123, 124). A well-functioning kidney transplant also restores and maintains a normal fluid homeostasis and partly helps to ensure normal blood pressure (125). Arterial hypertension is, however, approximately equally prevalent in transplanted patients, as is use of antihypertensive medication in patients on chronic HD (74, 126).

The outcome of patients who have received a kidney transplant is as such considerably better than the outcome of HD or PD patients, but no randomized controlled trials have objectively compared kidney transplantation to dialysis treatments. Of all chronic RRT patients, the ones selected to receive a kidney
transplant are in general younger and with fewer comorbidities than the ones who never receive a kidney transplant, and also possess other characteristics associated with favorable prognosis (127, 128).

2.2.2 SELECTION OF DIALYSIS MODALITY

The selection of a patient’s modality of chronic RRT requires thorough evaluation of both advantages and disadvantages, and the decision is affected by many factors, both treatment- and patient-related (129). Examples of patient-related factors include urgency of RRT start, the patient’s overall physical and mental state, severity of possible comorbidities, and socio-economic and occupational conditions (23). In addition, considerations on availability of local health care resources and varying experience in using different modalities are important.

RRT modalities which encourage maintaining the patient’s personal way of living and quality of life can be seen as the first choices in helping to preserve the patient’s autonomy and thus minimally disabling the patient, preventing him/her from living the kind of life he/she desires (119). On the other hand, modalities like CAPD, APD, and home-HD require independent initiative as well as the patient’s adopting and learning the modalities, and are therefore not applicable for all patients. While APD or home-HD often offer freedom from daytime dialysis and better suit relatively healthy patients still active in working life, in-center HD is often the only option for many of the patients, and especially for those with the most physical disability.

Selection of the RRT modality to be preferred varies greatly across the world especially due to uneven distribution of local resources and differences that modality causes in clinical practice (71). Furthermore, varying geographical circumstances may be important to take into consideration. In a setting where it is urgent to start chronic RRT, the modality chosen for the vast majority of patients is HD, due to its rather straight-forward approach and the relative technical ease with regard to its start and usually the excellent availability of the technique. When initiation of chronic RRT can be planned without any major hurry, there is a better chance to consider the suitability of other modalities. In these circumstances, PD is quite often the modality of choice. Whereas PD treatment may be suitable for up to 75% of patients starting chronic RRT, the actual incidence is much lower. The most common reasons are contraindications to PD (like prior major abdominal operations) and especially patients’ views of acceptable dialysis modality (130, 131). Worldwide distribution of HD and PD varies significantly between countries, from 97% in HD and 3% in PD in Japan, to 27% and 73% in Hong Kong (71). Although RRT modalities which support patient autonomy are usually considered the first option to offer to those capable of performing them, in a study exploring worldwide use of different RRT modalities in 2004, only approximately 11% of chronic RRT
patients were receiving PD, and only 0.4% home-HD (132). In geographically large countries with proportionally few nephrological centers in their vast rural areas, PD is, however, often an attractive home-dialysis modality. In many countries, kidney transplantation is quite commonly performed instead of any dialysis, but in countries like Finland, pre-emptive kidney transplantation is rather rare.

In most European countries and on day 91 after start of chronic dialysis treatment, the dialysis modality of those patients starting RRT in 2011 was some form of HD in 71 to 84% (65-110 pmp), PD in 10 to 20% (15-25 pmp) and kidney transplantation in 1 to 6% (4-10 pmp) of the patients, with significant variability between countries, especially for the two latter modalities (2). In 2013 in Finland, among 485 patients, the RRT modality by which chronic treatment was started was HD in 350 (72%), PD in 134 (28%) and pre-emptive kidney transplantation in one (1). In 2012, of all the Finnish PD patients, approximately 42% used CAPD and 58% APD (74).

2.3 SURVIVAL ON CHRONIC RENAL REPLACEMENT THERAPY

2.3.1 FACTORS ASSOCIATED WITH INCREASED MORTALITY

In patients on chronic RRT, various patient-level properties are related to survival. Such properties are many, and the most important has very commonly been patient age (6). Other factors often strongly associated with survival are serum albumin and certain comorbidities such as heart failure, cancer, and chronic infection/inflammation (9, 10, 61, 133, 134). For patients entering chronic RRT, the etiology of ESRD may also be a strong predictor of impaired survival; this applies, for instance, to type 2 diabetes and amyloidosis (11, 20, 135, 136).

Patient characteristics, their relation to survival, and comparison of survival between various patient groups are typically assessed in observational follow-up studies. In order to perform reliable survival analyses, it is vitally important to account for all possible effects on mortality of numerous patient- and treatment-related factors. This is especially important when comparing patient groups that differ with regard to frequency of the characteristics (61). Failing to perform comprehensive adjustment of these putative confounding factors will lead to false results (137).

2.3.2 PATIENTS WITH TYPE 1 DIABETES

Diabetes mellitus (types 1 and 2 combined) is the most important cause of ESRD in industrialized countries (2). In Finland, incidence of type 1 diabetes is among
the highest in the world (138). Great progress has occurred, however, in treatment of type 1 diabetes since the 1970s, with many forms of improved insulin regimens and intensified blood glucose monitoring, resulting in fewer episodes of hypo- and hyperglycemia, and closer-to-target blood glucose levels (139). Overall, all these improvements have diminished the frequency of diabetic nephropathy and of ESRD due to diabetic kidney disease (140). Moreover, the risk of Finnish patients with type 1 diabetes to develop ESRD has been diminishing over the past four to five decades (19). Whether progresses in overall management of type 1 diabetes could also reflect improved survival on chronic RRT is still largely unknown.

Survival of Danish patients with diabetes (types 1 and 2 combined) (21) and Finnish patients with type 2 diabetes (136) on chronic RRT has improved during recent decades. Furthermore, survival of patients with specifically type 1 diabetes as the etiology of ESRD has probably also improved (20, 141). However, conflicting results have also been published, showing no improvement in survival of this patient group (22).

Recently, in Finnish ESRD patients with type 1 diabetes, certain comorbidities (for instance, heart failure and peripheral vascular disease), have been associated with increased mortality (8). In addition, a higher number of comorbidities in these patients is correlated with higher risk of death (8). Study of the long-term survival of Finnish patients with type 1 diabetes on RRT has been neglected.

2.3.3 DIALYSIS MODALITY AND SURVIVAL

For decades, nephrologists have puzzled over the question whether either of the main dialysis modalities is superior to the other with regard to survival in chronic use (142).

HD and PD techniques differ so much that these techniques per se could be expected to cause survival difference. We know that the frequency of adverse events between dialysis modalities differs, and this could alter patient survival (142, 143). On HD, on the one hand there are non-infectious complications relating to catheter insertion (144), and on the other, inadequate sterility in treatment procedures causing a higher risk for catheter-related septicemia and other infections (145). In addition, on HD hypotension and potentially hazardous electrolyte disturbances are rather frequent (146). On PD, risk for peritonitis related to the treatment is clearly elevated, with about 0.03 to 0.20 episodes per patient-year depending on the microorganism (147, 148). Furthermore, almost constant exposure to glucose-containing PD fluids and loss of plasma albumin into PD fluids are subjects of concern (143, 149).

Survival on chronic dialysis is associated with the years spent on dialysis treatment, with increasing risk with longer duration on dialysis, but the difference in death risk between dialysis modalities seems not to be linear (39, 41, 43-45).
According to others’ results, mortality risk is lower during the first one to two years on PD, but after that, the risk would equal that on HD (39, 40). Furthermore, according to some investigators, the risk is elevated in those patients who change their initial dialysis modality (39, 42).

Many patient characteristics are associated with survival. Of such characteristics, especially age, serum albumin, and certain comorbidities (such as heart failure) have been strong prognostic factors (8, 58, 150). In patients on chronic RRT, many of the same characteristics are related to survival as in the non-ESRD population (150). In addition, comorbidities such as ischemic heart disease and cardiac left ventricular hypertrophy (9, 133, 134), and causes of ESRD such as type 2 diabetes and amyloidosis (11, 135, 136, 151) are portents of increased mortality risk on RRT. The magnitude of risk associated with a comorbidity also seems to vary according to dialysis modality (38-41, 152). The death risk caused by heart failure is higher on HD than on PD (9, 133). PD, on the other hand, has seemed to pose a lower risk in young patients without comorbidities (39, 40) and a higher risk in older patients with diabetes (41, 47). On the other hand, for non-diabetic patients, no survival difference is apparent between continuous ambulatory PD and HD (46).

Survival on chronic RRT is also likely to depend on whether a patient has received a kidney transplant (153). To take this into account in survival analyses is complex, however, as the frequency of transplantations is very different between HD and PD patients (15, 154, 155); comparison between these patient groups would therefore require either a randomized study setting or otherwise an exceptionally good balance in patient characteristics.

To date, only one randomized study has compared survival of patients on chronic dialysis between HD and PD (156). That study was prematurely halted because too few patients were recruited, and it failed to achieve sufficient statistical power. All the other studies published in the field have been observational and showed either conflicting results or no significant superiority of one modality over another (38-56). Thus, there still has been no conclusive answer to whether any survival advantage results from either main dialysis modality when used as the first-line chronic dialysis therapy.

**2.3.4 PRE-ESTIMATION OF MORTALITY RISK**

A large number of registries collect information on chronic patients and their illnesses. The quality of registry data is critical: the more accurate and comprehensive the data, the more reliable the study results based on them. Importantly, it is crucial for the data to include the most important factors relating to the outcome under investigation. In Finland, the Registry for Kidney Diseases has an exceptionally complete coverage of Finnish nephrological units and ESRD patients who have entered chronic RRT (1).
Patient- and treatment-related factors associated with patient survival have been used in constructing mathematical formulae to estimate individual mortality risk (137). These formulae are mathematical algorithms which allow incorporation of a minimal number of factors, each of which contributes independent predictive information. These algorithms can then serve as models to estimate patient-level mortality risk.

One of the first and most often applied models has been the Charlson Comorbidity Index (157), and for ESRD patients its modified version (158). Many similar tools, also ones taking into account factors other than comorbidities, have been constructed by several research teams in various countries (62-70). These tools were in most cases based on administrative or registry data derived from incident ESRD populations. A typical method to design a model has been to select a cohort of ESRD patients who have recently entered chronic RRT (typically within three months) and to calculate predictive probabilities of various patient characteristics by choosing the ones most relevant to the population investigated (137). Following this, a cohort is typically divided into two: a training group used only for model development, and an internal validation group used only for assessing the predictive ability of the model.

This predictive ability depends on two main properties: its performance in calibration (usually assessed by the Hosmer-Lemeshow test) and discrimination (often assessed by a c-statistic, area under the receiver operating characteristic curve [AUC]). In final prediction models, especially the latter performance (AUC) has been widely employed (137). A c-statistic (AUC) of 0.5 would mean no predictive ability of the model, and an AUC of 1.0, perfect predictive ability. Most studies reach an AUC between 0.72 and 0.84 for one-year prediction of death risk and an AUC between 0.67 and 0.75 for two-year prediction. An AUC value of 0.75 has been considered sufficient by the majority (64-70, 159, 160). Performance in calibration can be done by comparing average predicted probabilities of death to observed mortality, sometimes shown graphically in articles. A non-significant P value in the Hosmer-Lemeshow test would indicate good calibration, that is, good resemblance between predicted and observed mortality.

In a study by Mauri and coworkers, 5,738 incident Catalan HD patients from 1997 to 2003 were randomly divided into development (60%) and validation (40%) groups (64). The investigators build a one-year predictive model with 10 variables and reached an AUC of 0.78. Another study focusing on one-year mortality after start of chronic RRT was by Quinn and colleagues who investigated 16,025 incident Canadian dialysis patients (HD 76%, PD 24%) from 1998 to 2005 (67). With diverse statistical methods, they built a predictive model with an AUC of 0.76 and a summary risk score including data on socioeconomic status and a wide range of comorbidities. The final mortality prediction model comprised 15 variables; it may in that respect be less convenient for everyday clinical work.
Other large studies have aimed at longer than one-year prognostication. Liu and colleagues investigated very large incident and prevalent US dialysis populations (over 240,000 in total, the proportions of HD/PD not reported) from 1999 to 2001, with a follow-up reaching 2.5 years (66). By inclusion of data on 11 comorbid illnesses, they developed a comorbidity score. The performance of the model exceeded that of the earlier Charlson Comorbidity Index, but discrimination could still only reach an AUC of 0.67. The quality of that study has been questioned based on possible weaknesses in data sources and its including only patients who survived for over nine months on RRT. The model was also developed to predict length and number of hospitalizations and help in medical cost analyses and was reported to perform well for these tasks. A three-year model was built by Wagner and colleagues using data from an incident UK dialysis population of 5,447 (HD approx. 70%, PD approx. 30%) during 2002–2004 (68). A validation cohort of 1,816 was internal, but almost half of the original incident patients were excluded due to missing data. This model was able to differentiate patients in four levels of mortality risk (low – intermediate – high – very high) with an AUC of 0.73 in the validation group.

Another model aiming at long-term prognostication was developed by Hemke and colleagues using Dutch registry data on 13,868 patients who entered RRT from 1995 to 2005 (69). Their 10-year model performed similarly to the models described above (AUC 0.72), and they used internal validation. In addition to these studies done at a national level, a multinational study based on ERA-EDTA Registry involving 793 centers from 37 countries (including a total of 2,310 patients) created two novel prognostic models (63). Their models performed better in longer (five-year) than shorter (one-year) prediction.
3 AIMS OF THE STUDY

The main aim of this study was to investigate factors associated with mortality of patients on chronic RRT. In more detail, we targeted the following aims:

1. To investigate whether survival of patients with type 1 diabetes has improved since 1980, and to which factors any possible change could be attributed (I)

2. To explore the association between eGFR decline patterns and long-term survival of all patients entering chronic RRT by using multiple predialysis measurements of serum creatinine to calculate eGFR slope (II)

3. To investigate the association between dialysis treatment modality and survival on chronic RRT (i.e., to compare patients starting with HD to those starting with PD), and to learn whether this association varies between major subgroups of patients (III)

4. After analyzing which factors are the most important for survival of patients on chronic RRT, to use this information to construct a mathematical risk-stratification model to estimate patient survival on chronic RRT (IV)
4 SUBJECTS AND METHODS

4.1 DATA SOURCE

Data on subjects of all the studies in the thesis came from the Finnish Registry for Kidney Diseases, a national registry recording information on all patients entering chronic RRT in Finland since 1965 (1). This registry is maintained by the Finnish Kidney and Liver Association and financed by the Finnish government.

Data of the registry are provided directly by the Finnish nephrological care-providers, the treating nephrologists, and the units delivering nephrological care; data and patient coverage of the registry is therefore considered exceptionally reliable. This information is collected on regular basis and includes data on demographics (age and gender), date of RRT start, modality of RRT, comorbidities, medication, and results of pre-defined laboratory tests. Importantly, extensive data were collected in 1998 on, for instance, development of serum creatinine values before patients’ entering chronic RRT, and, since 2000, comprehensively on comorbidities at start of RRT. Renal disease diagnoses have earlier been stored as International Classification of Diseases (ICD) -9 codes and more recently as ICD-10 codes. All patients entering chronic RRT provide written informed consent and permission to use the data anonymously in registry reports and for research purposes. Thus, no additional approval of any ethics committees was required for the observational studies of the thesis.

In Study III, we also used data retrieved from the Finnish Kidney Transplant Registry, which is maintained by the Kidney Transplantation Unit of Helsinki University Hospital. This registry includes comprehensive information on waitlisted and transplanted patients.

Table 2 Subjects of the four studies included in the thesis.

<table>
<thead>
<tr>
<th></th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>3,160</td>
<td>319</td>
<td>4,463</td>
<td>6,103</td>
</tr>
<tr>
<td>Follow-up until</td>
<td>31 Dec 2007</td>
<td>31 Dec 2008</td>
<td>31 Dec 2009</td>
<td>Training group: 1 or 2 years after the start of dialysis Validation group: 31 Dec 2013</td>
</tr>
<tr>
<td>Age, years</td>
<td>All</td>
<td>≥ 20</td>
<td>≥ 20</td>
<td>≥ 18</td>
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</table>

RRT, renal replacement therapy
4.2 SUBJECTS AND DESIGNS OF THE FOUR STUDIES

4.2.1 STUDY I

In Study I, we investigated factors affecting survival of patients with type 1 diabetes on chronic RRT. We included an incident cohort of all 1,604 patients with type 1 diabetes and all 1,556 with glomerulonephritis as the cause of ESRD who had entered chronic RRT from 1 January 1980 to 31 December 2005 (Table 2). They were followed from the first day of RRT until death or the end of follow-up on 31 December 2007, or until recovery of kidney function, or until they had moved abroad or were lost to follow-up (Table 3). We used the cohort with glomerulonephritis as a control group to represent primary renal disease to allow us to perform a comparison between the impact of RRT-associated factors and the impact of factors associated with diabetes care.

Table 3 Baseline characteristics of the patient populations in Studies I-IV.

<table>
<thead>
<tr>
<th></th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>1,604¹</td>
<td>319</td>
<td>4,463</td>
<td>4,335 (training group)</td>
</tr>
<tr>
<td></td>
<td>1,556²</td>
<td></td>
<td></td>
<td>1,768 (validation group)</td>
</tr>
<tr>
<td>Median age at RRT start, years</td>
<td>41.0¹</td>
<td>60.0</td>
<td>62.4</td>
<td>62.3 (training)</td>
</tr>
<tr>
<td></td>
<td>53.1²</td>
<td></td>
<td></td>
<td>64.1 (validation)</td>
</tr>
<tr>
<td>Males, %</td>
<td>63.8¹</td>
<td>60.3</td>
<td>63.8</td>
<td>63.5 (training)</td>
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<tr>
<td></td>
<td>71.8²</td>
<td></td>
<td></td>
<td>67.8 (validation)</td>
</tr>
<tr>
<td>Median follow-up, years</td>
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<td>6.0</td>
<td>2.8</td>
<td>N.A.</td>
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<tr>
<td>Maximum follow-up, years</td>
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<td>11</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Died during follow-up, n</td>
<td>1,047¹</td>
<td>214</td>
<td>1,887</td>
<td>1 year: 597</td>
</tr>
<tr>
<td></td>
<td>823²</td>
<td></td>
<td></td>
<td>2 years: 1,080</td>
</tr>
<tr>
<td>Censored patients, n</td>
<td>557¹</td>
<td>243</td>
<td>2,576</td>
<td>1 year: 3,738</td>
</tr>
<tr>
<td></td>
<td>733²</td>
<td></td>
<td></td>
<td>2 years: 3,255</td>
</tr>
<tr>
<td>Alive at end of follow-up</td>
<td>548¹</td>
<td>235</td>
<td>2,494</td>
<td>1 year: 3,674</td>
</tr>
<tr>
<td></td>
<td>719²</td>
<td></td>
<td></td>
<td>2 years: 3,172</td>
</tr>
<tr>
<td>Regained kidney function</td>
<td>5¹</td>
<td>8</td>
<td>78</td>
<td>1 year: 63</td>
</tr>
<tr>
<td></td>
<td>8²</td>
<td></td>
<td></td>
<td>2 years: 81</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>0¹</td>
<td>0</td>
<td>1</td>
<td>1 year: 0</td>
</tr>
<tr>
<td></td>
<td>2²</td>
<td></td>
<td></td>
<td>2 years: 1</td>
</tr>
<tr>
<td>Moved abroad</td>
<td>4¹</td>
<td>0</td>
<td>3</td>
<td>1 year: 1</td>
</tr>
<tr>
<td></td>
<td>4²</td>
<td></td>
<td></td>
<td>2 years: 1</td>
</tr>
</tbody>
</table>

RRT, renal replacement therapy
¹Patients with type 1 diabetes
²Patients with glomerulonephritis
During this time-period, a total of 8,719 patients started chronic RRT, and of these the ESRD cause was for 18.4% type 1 diabetes and for 17.8% glomerulonephritis. The ESRD diagnosis was confirmed by kidney biopsy in 80 (5%) patients with type 1 diabetes and 980 (63%) with glomerulonephritis. In the glomerulonephritis group, the frequency of kidney biopsies clearly increased over the years, reaching 73 to 85% during 1995–2005, whereas in the type 1 diabetes group, the frequency remained low. It has been, and still is, a widely accepted practice not to perform kidney biopsies in patients with type 1 diabetes if they show, in addition to nephropathy, also signs of other microvascular end-organ damage, such as diabetic retinopathy.

In addition to comparing the two main ESRD groups, we divided the patients into four age-groups based on age at start of RRT: under 35 (444 patients), from 35 to 44 (586), from 45 to 54 (383) and 55 or over (191). Furthermore, we divided the study period into five intervals: 1980–1984, 1985–1989, 1990–1994, 1995–1999, and 2000–2005.

4.2.2 STUDY II

Study II was designed to investigate patterns of eGFR slope before entering chronic RRT and related survival subsequently on RRT. For that aim we studied all incident patients 20 years or older having started chronic RRT from 1 January 1998 to 31 December 1998 (Table 2). These patients were followed from their first day of dialysis until death or the end of follow-up on 31 December 2008, or until recovery of kidney function, or until the patients had moved abroad or were lost to follow-up (Table 3).

These patients were grouped into tertiles according to eGFR slope, which was based on three creatinine measurements preceding commencement of RRT; those 107 patients with the most rapid decline (over 8.5 ml/min/1.73 m²/year), the intermediate group of 107 (decline 3.4–8.5 ml/min/1.73 m²/year), and the 105 patients with the slowest decline (less than 3.4 ml/min/1.73 m²/year). These data were derived from a specific questionnaire asked to be filled out for each of the 457 new patients entering chronic RRT in 1998 in Finland. The questionnaire went to all nephrologists who treated these patients and surveyed comprehensive information including data on specific laboratory results, among which were values for serum creatinine during the 12 months prior to RRT start. Of the total 457 patients, the questionnaire was sufficiently completed for 94%, and of these, those eight who regained kidney function and those 23 who died within the first three months were excluded.

We used data on serum creatinine measured at three time-points: approximately 12 months, three months and one to two weeks prior to start of chronic RRT. Completeness of data on creatinine increased towards the start of RRT: for 329,
356, and 365 patients at those three time-points. At all the three time-points, we had data on the 319 patients (70% of those who initially entered RRT) who were finally included in the study.

For estimation of GFR, we used the Modification of Diet in Renal Disease (MDRD) formula (eGFR = 175 x [plasma creatinine in µmol/L/88.4]^{1.154} x age^{-0.203} for males, and this equation multiplied by 0.742 for females) (161). In order to calculate the slope of eGFR for each patient, we applied a linear regression formula: (eGFR = a + β x T). In the formula “a” represented eGFR at start of RRT, “β” (beta) stood for slope, and “T” the time (in years) from the first creatinine measurement to start of RRT. As a result, we were able to obtain annual eGFR slopes (in ml/min/1.73 m²), based on which the abovementioned patient grouping was then done.

4.2.3 STUDY III

Study III compared survival of chronic RRT patients according to initial dialysis modality, that is, HD versus PD. The time-point of chronic RRT was set to 91 days after the first dialysis treatment, as by that time (approximately three months) the intended chronic dialysis modality has usually been established. Our study population was a cohort consisting of all 4,754 patients 20 years or older who started chronic RRT from 1 January 2000 to 31 December 2009 (Table 2). Of these, we excluded 291 patients for these reasons: 137 had died before 91 days on RRT, for 15 their dialysis treatment had been discontinued, eight had regained their kidney function, 37 had received a kidney transplant before 91 days on RRT, and 94 had been less than 91 days on dialysis before the end of follow-up. Subsequently, 4,463 were included in the final analyses. These patients were followed from the day of first dialysis treatment until death, recovery of kidney function, moving abroad, loss to follow-up, or end of the follow-up period on 31 December 2009 (Table 3).

We used two designs of approach in grouping the patients: 1) an intention-to-treat approach (primary analysis), in which we divided the patients into two groups (HD or PD) according to their dialysis modality on day 91, and 2) an as-treated approach (secondary analysis), in which the patients were divided into four groups according to dialysis modality on day 91, and additionally, whether they stayed permanently in that initial modality until kidney transplantation or end of follow-up, or if they changed to the other dialysis modality. Accordingly, the established four modality groups were 1) those exclusively on HD, 2) those exclusively on PD, 3) those who changed from HD to PD, and 4) those who changed from PD to HD. This grouping allowed us a comparison of patients who had been exclusively on PD to those who had been exclusively on HD.
In both approaches, the HD group included in-center HD for 3,122 and HDF for 19, and home-HD for 105; the PD group comprised patients with any form of PD treatment (667 on continuous ambulatory PD, 535 on automated PD, and 15 on intermittent PD).

Due to the very different frequencies between HD and PD patients of transplant waitlisting and transplantations performed, and to address the potential confounding effect of these differences, we adjusted for kidney transplant waitlist status at three months from RRT start. We also censored at the time of kidney transplantation, but only as an additional analysis approach. Furthermore, as an alternative to censoring, we performed adjustment for transplantation as a time-dependent variable, resulting in a very similar outcome to that of censoring at transplantation.

4.2.4 STUDY IV

In Study IV, we aimed to construct mathematical algorithms for prediction of one- and two-year all-cause mortality of patients starting chronic RRT. These algorithms would include the most important factors associated with survival, and be chosen based on analyses of data from the Finnish Registry for Kidney Diseases.

In order to construct the two prediction models (one- and two-year mortality), we chose a training and a validation group. The former consisted of all 4,341 incident patients 18 years or older who entered chronic RRT from 1 January 2000 to 31 December 2008, from among whom we removed the six patients with pre-emptive kidney transplantation (Table 2). Of note, we did not include any patients who were able to withdraw from dialysis during the first three months on dialysis, because they were not considered as chronic RRT patients. These 4,335 patients were followed from the first day of dialysis until death within one or two years, until recovery of kidney function after three months from RRT start, or moving abroad, loss to follow-up, or end of follow-up period (Table 3).

The validation group comprised all 1,770 patients 18 years or older who entered chronic RRT from 1 January 2009 to 31 December 2012, namely coming from a later period than the training group; this enabled us to have an external cohort exclusively used for validation of the final models. The two patients having had transplantation as their first RRT modality were excluded. We followed survival of these patients until 31 December 2013. We therefore could perform follow-up of one-year survival for the whole validation group, but of two-year survival only for those 1,341 who started dialysis at the latest on 31 December 2011.

On the basis of the literature, clinical expertise, and data availability in the Registry, we selected a large number, 32, of variables as candidates to be tested for their predictive performance (see list in Table 1 of the Study IV original publication). Data were unavailable to varying degrees depending on the variable
in question, and of the variables chosen for the final models were as follows: age at RRT start 0%, ESRD diagnosis 0%, albumin 4%, phosphorus 3%, C-reactive protein 20%, heart failure 9%, peripheral vascular disease 6%, and peripheral vascular disease with limb amputation 7%.

4.3 STATISTICAL ANALYSES

Comparisons between groups were performed with the chi-square test for categorical variables and the Mann-Whitney U- or Kruskal-Wallis test for continuous variables. We calculated survival probabilities with the Kaplan-Meier method, with death as the event, and patients were censored according to study-specific inclusion and exclusion criteria. Median survival times were estimated from the Kaplan-Meier curves, and differences in survival probabilities between groups were assessed by the log rank test. We used Cox proportional hazards regression to perform multivariable modeling of survival probabilities. When studying comorbidities in multivariable analysis, we used the assumption that missing data equals absence of comorbidity (Study II). In Study III, we employed both intention-to-treat and as-treated analysis methods. Furthermore, in Study III, we tested proportional hazards assumptions in the multivariable Cox model by calculating Schoenfeld residuals according to dialysis modality and correlating these with time of follow-up. A non-significant correlation indicated that the proportional hazards assumptions were not violated. Proportionality of hazards was also evaluated by studying the interaction of dialysis modality and time of follow-up. Two-sided p-values lower than 0.05 were considered statistically significant and lower than 0.001 highly significant. All first- and second-degree interactions between the explanatory variables considered relevant to the results were tested in the Cox model-building (Study II). In Study III, to avoid type I error due to multiple testing, a two-sided p-value lower than 0.01 was considered statistically significant in the interaction analyses. Due to missing data in the original Registry database, and in order to have no biased analysis results because of exclusion of a large number of patients, we performed multiple imputation for missing data (in Studies III and IV) in which the explanatory variables (and not the outcome variable) served to impute missing values. The final multivariable model was pooled from five imputed datasets.

In Study IV, prediction algorithms were developed with use of multivariable logistic regression with the binary outcome of death or not within one or two years from start of RRT. The Hosmer-Lemeshow (goodness-of-fit) test was used to assess calibration and the c-statistic (AUC) for discrimination. To detect non-linearity between continuous predictors and the outcome, we categorized continuous variables into three to six groups and modeled the categorical variables
in univariate logistic regression analysis. If we observed non-linearity, we first evaluated logarithmic transformation of the predictor and then compared it to no transformation and the categorical variable. Subsequently, we calculated predicted probabilities and constructed graphs for continuous variables against probability of mortality, followed by choosing the best-fitting transformation (either linear, logarithmic, or group variable) according to the -2 Log likelihood- and the Hosmer-Lemeshow test. We calculated the predicted probabilities with the following equation:

Predicted probability = 1 / (1 + e^{-\text{logit}}), where e is the base of the natural logarithm 2.71828, and logit is defined as:

\[ \text{logit} = \beta_0 + \beta_1 \chi_1 + \beta_2 \chi_2 + \ldots + \beta_m \chi_m, \]

where \( \beta_0 \) is the constant of the logistic regression equation, and \( \beta_1 \) to \( \beta_m \) represent regression coefficients of the variables \( \chi_1 \) to \( \chi_m \).

The regression coefficients can be calculated by taking the natural logarithm of the odds ratios for survival probability. With this equation, it is possible to calculate predicted probability of death for each patient.

Further, in Study IV, we used forward and backward stepwise procedures to select the variables among the 32 original ones with the strongest effect on survival. After interim analyses, only variables with a p-value of 0.05 or lower were taken to the next step (leaving 15 in the one-year model and 13 in the two-year model), followed by another assessment in a logistic regression model, after which (in order of statistical significance) variables were further evaluated in 4-15 variable combinations. These combinations were compared for predictive performance (discrimination and calibration) within the training group. The final predictive models contained only highly significant (p<0.001) variables: seven in the one-year model and six in the two-year model.

For statistical analyses we used SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) and versions 18 and 20 (IBM Inc., Armonk, NY, USA) and Stata 12 (StataCorp LP, College Station, TX, USA). All possible first-degree (Studies I to IV) and second-degree (Studies I and II) interactions between the explanatory variables were considered in the building of the multivariable regression models.
5 RESULTS

Table 3 describes baseline characteristics of the final patient populations included in the four (I-IV) studies (Table 3).

5.1 SURVIVAL OF PATIENTS WITH TYPE 1 DIABETES RECEIVING RENAL REPLACEMENT THERAPY IN 1980–2007

Many changes in characteristics of patients with type 1 diabetes entering chronic RRT have taken place. Median age at initiation of RRT increased from 34.8 years in 1980–1984 to 44.6 years in 2000–2005 (p<0.001). The proportion of PD as the first RRT modality decreased from 55% to 48%. Frequency of kidney transplantation performed within two years from RRT start diminished to 35% in 2000–2005, whereas it was 60% in 1980–1984.

5.1.1 CRUDE SURVIVAL

During follow-up, of the total 1,604 patients with type 1 diabetes, 1,047 (65.3%) died. Median survival time increased significantly from 3.6 years (95% CI 2.50-4.70) in the 1980–1984 cohort to 7.24 years (95% CI 5.74-8.74) in the 1995–1999 cohort (Figure 1). In patients who started RRT during 2000–2005, median survival time was over eight years and therefore could not be precisely calculated because it was longer than the maximal follow-up time. Furthermore, median survival times increased significantly in all age-groups. From 1980–1984 to 2000–2005, absolute risk of death within five years from RRT start decreased from 58% to 38% (Figure 2), with the unadjusted relative risk (RR) of death diminishing to 55% in patients during 2000–2005 compared to the cohort of 1980–1984 (Table 4). In age subgroups, the corresponding risk ratios were even lower (0.31-0.38; the lowest in patients under 35 years and the highest in patients 55 years or above), indicating the confounding effect of age. In all cohorts combined, the risk of death increased by 4.2% (95% CI 3.4-4.7) per year of age at start of RRT.
Figure 1  Survival of patients with type 1 diabetes entering chronic renal replacement therapy (RRT) according to start period of RRT.

Figure 2 Absolute risk (%) of death within five years from start of chronic renal replacement therapy (RRT) according to start period of RRT, in patients with type 1 diabetes (blue bars) and patients with glomerulonephritis (orange bars).
Table 4 Relative risk (RR) of death in patients with type 1 diabetes according to start period of chronic renal replacement therapy (RRT).

<table>
<thead>
<tr>
<th>RRT start period</th>
<th>Unadjusted RR (95% CI)</th>
<th>Adjusted(^1) RR (95% CI)</th>
<th>Adjusted(^2) RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980–1984(^3)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1985–1989</td>
<td>0.87 (0.72-1.06)</td>
<td>0.72 (0.59-0.87)</td>
<td>0.64 (0.52-0.77)</td>
</tr>
<tr>
<td>1990–1994</td>
<td>0.70 (0.58-0.85)</td>
<td>0.53 (0.44-0.65)</td>
<td>0.44 (0.36-0.54)</td>
</tr>
<tr>
<td>1995–1999</td>
<td>0.66 (0.54-0.81)</td>
<td>0.43 (0.35-0.52)</td>
<td>0.33 (0.27-0.41)</td>
</tr>
<tr>
<td>2000–2005</td>
<td>0.55 (0.44-0.68)</td>
<td>0.33 (0.26-0.41)</td>
<td>0.23 (0.19-0.29)</td>
</tr>
</tbody>
</table>

CI, confidence interval
\(^1\)Adjusted for age at RRT start and for gender
\(^2\)Adjusted for age at RRT start and for gender, initial mode of dialysis, and having or not having received a kidney transplant within two years of RRT start
\(^3\)Reference group


Of the 1,556 patients with glomerulonephritis, 823 (52.9%) died during follow-up, and compared to patients with type 1 diabetes, their median survival time was significantly longer, but showed no significant increase; the five-year risk of death in 1980–1984 was 29% (95% CI 0.23-0.35) and was still the same in 2000–2005 (Figure 2). In unadjusted analysis and compared to the cohort of 1980–1984, the RR of death in the 2000–2005 cohort was non-significantly lower, 0.88 (95% CI 0.68-1.14) (Table 5).

Table 5 Relative risk (RR) of death in patients with glomerulonephritis according to start period of chronic renal replacement therapy (RRT).

<table>
<thead>
<tr>
<th>RRT start period</th>
<th>Unadjusted RR (95% CI)</th>
<th>Adjusted(^1) RR (95% CI)</th>
<th>Adjusted(^2) RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980–1984(^3)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1985–1989</td>
<td>1.01 (0.82-1.25)</td>
<td>0.86 (0.69-1.06)</td>
<td>0.76 (0.61-0.94)</td>
</tr>
<tr>
<td>1990–1994</td>
<td>1.21 (0.98-1.50)</td>
<td>0.72 (0.58-0.90)</td>
<td>0.60 (0.48-0.75)</td>
</tr>
<tr>
<td>1995–1999</td>
<td>1.17 (0.93-1.46)</td>
<td>0.59 (0.47-0.74)</td>
<td>0.49 (0.38-0.62)</td>
</tr>
<tr>
<td>2000–2005</td>
<td>0.88 (0.68-1.14)</td>
<td>0.37 (0.28-0.49)</td>
<td>0.30 (0.23-0.40)</td>
</tr>
</tbody>
</table>

CI, confidence interval
\(^1\)Adjusted for age at RRT start and for gender
\(^2\)Adjusted for age at RRT start and for gender, initial mode of dialysis, and having or not having received a kidney transplant within two years of RRT start
\(^3\)Reference group

5.1.2 ADJUSTED SURVIVAL

When adjusting for age and gender in survival analyses, an even more significant improvement in survival was detectable in patients with type 1 diabetes. Compared to 1980–1984, patients starting RRT in 2000–2005 had a RR of death of only 0.33 (Table 4). With further adjustment for initial mode of dialysis and whether a patient had received a kidney transplant within two years of RRT start, the corresponding RR fell to 0.23.

Similarly, in patients with glomerulonephritis, a significant improvement in prognosis occurred, with a RR of 0.30 in 2000–2005 compared to 1980–1984 (Table 5).

5.1.3 COMPARISON OF SURVIVAL BETWEEN PATIENTS WITH TYPE 1 DIABETES AND GLOMERULONEPHRITIS

To compare the magnitude of change detectable in survival of both patient groups, we performed interaction analysis between the patient groups and the RRT start period, with adjustment for age, gender, RRT mode, and kidney transplantation status at two years from RRT start. This revealed that the RR of death decreased more in patients with type 1 diabetes than in patients with glomerulonephritis (p=0.007). In 1980–1984, patients with type 1 diabetes had a 3.5-fold higher risk of death than did glomerulonephritis patients, and this risk had diminished to 2.7-fold in the 2000–2005 cohort.

5.2 DECLINE IN GLOMERULAR FILTRATION RATE DURING PRE-DIALYSIS PHASE AND SURVIVAL ON CHRONIC RENAL REPLACEMENT THERAPY

5.2.1 FACTORS ASSOCIATED WITH RAPID eGFR DECLINE

Dividing the 319 patients into tertiles according to eGFR decline rate during the year preceding start of chronic RRT clearly separated the fastest decliners from the two slower groups (Figure 3). Significant differences in patient characteristics emerged between the three eGFR decline groups, especially after separating the fastest decliners from the other groups. The fastest decliners were younger and had a lower serum albumin concentration (Table 6). In addition, frequency of males and type 1 diabetes were both clearly higher among the fast decliners, and nephrological follow-up had been shorter for them.
Table 6  Characteristics of patient groups according to estimated glomerular filtration rate (eGFR) decline rate during the year before starting chronic renal replacement therapy (RRT). Variables expressed as median (interquartile range) unless otherwise stated.

<table>
<thead>
<tr>
<th>Variables expressed as median (interquartile range)</th>
<th>Slowest (n=105)</th>
<th>Intermediate (n=107)</th>
<th>Fastest (n=107)</th>
<th>All (n=319)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (years)</td>
<td>64 (53-72)</td>
<td>56 (46-70)</td>
<td>54 (41-65)</td>
<td>60 (47-69)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Males, %</td>
<td>49</td>
<td>63</td>
<td>70</td>
<td>61</td>
<td>0.005</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26 (23-30)</td>
<td>25 (22-27)</td>
<td>24 (22-27)</td>
<td>25 (22-28)</td>
<td>0.028</td>
</tr>
<tr>
<td>Blood hemoglobin, g/L</td>
<td>108 (97-120)</td>
<td>105 (94-118)</td>
<td>102 (92-111)</td>
<td>104 (94-117)</td>
<td>0.039</td>
</tr>
<tr>
<td>Serum albumin, g/L</td>
<td>35 (32-38)</td>
<td>34 (30-38)</td>
<td>30 (26-35)</td>
<td>34 (29-37)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Nephrological follow-up, months</td>
<td>47.5 (20.2-92.3)</td>
<td>49.9 (16.2-92.7)</td>
<td>16.3 (7.6-33.6)</td>
<td>32.7 (11.2-81.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Residual renal function, diuresis, L/day</td>
<td>1.8 (1.2-2.2)</td>
<td>1.8 (1.2-2.4)</td>
<td>1.6 (1.0-2.2)</td>
<td>1.7 (1.1-2.2)</td>
<td>0.332</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>7.8 (6.2-10.0)</td>
<td>6.7 (5.3-8.2)</td>
<td>6.8 (5.2-8.5)</td>
<td>7.1 (5.6-8.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>eGFR approx. 3 months prior to RRT start, mL/min/1.73 m²</td>
<td>8.1 (7.0-10.1)</td>
<td>8.8 (7.3-11.1)</td>
<td>11.5 (8.6-16.5)</td>
<td>9.2 (7.3-11.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>eGFR approx. 12 months prior to RRT start, mL/min/1.73 m²</td>
<td>9.3 (7.6-12.1)</td>
<td>11.6 (10.5-14.2)</td>
<td>19.8 (15.8-29.5)</td>
<td>13.3 (9.7-18.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ESRD diagnosis, %</td>
<td>15</td>
<td>12</td>
<td>13</td>
<td>14 (43)</td>
<td>0.001</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>15</td>
<td>12</td>
<td>13</td>
<td>14 (43)</td>
<td>0.001</td>
</tr>
<tr>
<td>Polycystic degeneration</td>
<td>15</td>
<td>17</td>
<td>4</td>
<td>12 (38)</td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>11</td>
<td>27</td>
<td>32</td>
<td>24 (75)</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>16</td>
<td>12</td>
<td>18</td>
<td>15 (49)</td>
<td></td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>12</td>
<td>5</td>
<td>2</td>
<td>6 (20)</td>
<td></td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>6</td>
<td>9</td>
<td>8</td>
<td>8 (25)</td>
<td></td>
</tr>
<tr>
<td>Other or undefined</td>
<td>24</td>
<td>18</td>
<td>23</td>
<td>22 (69)</td>
<td></td>
</tr>
</tbody>
</table>

ESRD, end-stage renal disease

eGFR decline rate tertiles (mL/min/1.73 m²/year): slowest = less than 3.4, intermediate = 3.4-8.5, fastest = over 8.5.

(Reproduced and adapted from Mikko Haapio et al. Decline in Glomerular Filtration Rate During Pre-dialysis Phase and Survival on Chronic Renal Replacement Therapy. Nephrology Dialysis Transplantation (2012) 27 (3): 1157-1163. By permission of Oxford University Press on behalf of ERA-EDTA.)
Figure 3  Estimated glomerular filtration rate (eGFR) values at the three measurement points in Study II. Patients divided according to the tertiles of eGFR decline rate (x-axis) during the year preceding start of chronic renal replacement therapy; eGFR (y-axis) expressed as ml/min/1.73 m².

Among the patients with a slower eGFR decline, pyelonephritis and polycystic kidney degeneration were more frequent than in the fastest eGFR decliners. Of note, frequency of kidney transplantation did not differ between the eGFR decline tertiles. In multivariable analysis, use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and male gender (in this order of statistical significance) remained independent predictors of rapid eGFR decline.

5.2.2 COMORBIDITIES AND eGFR DECLINE RATE

When comparing the three groups and without adjustment, no significant differences in the distribution of non-renal diagnoses nor the number of comorbidities were detectable (Table 7). With adjustment for age, however, angina pectoris and left ventricular hypertrophy were more frequent among the patients with the fastest eGFR decline. Having one or more comorbidities was also more common in that group.
Table 7  Comorbidities of patients according to estimated glomerular filtration rate (eGFR) decline rate during the year before starting chronic renal replacement therapy. Variables expressed as percentage within eGFR tertile.

<table>
<thead>
<tr>
<th>Comorbidity, diagnosis</th>
<th>Slowest (n=105)</th>
<th>Intermediate (n=107)</th>
<th>Fastest (n=107)</th>
<th>All (n=319)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina pectoris</td>
<td>25</td>
<td>34</td>
<td>31</td>
<td>30 (94)</td>
<td>0.337</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>15</td>
<td>12</td>
<td>18</td>
<td>15 (47)</td>
<td>0.514</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>7</td>
<td>6</td>
<td>8</td>
<td>7 (22)</td>
<td>0.728</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>33</td>
<td>46</td>
<td>42</td>
<td>41 (113)</td>
<td>0.162</td>
</tr>
<tr>
<td>Cancer</td>
<td>6</td>
<td>3</td>
<td>6</td>
<td>5 (15)</td>
<td>0.507</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comorbidity, amount</th>
<th>Slcest = less than 3.4, intermediate = 3.4-8.5, fastest = over 8.5.</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>51</td>
</tr>
<tr>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>2 or more</td>
<td>23</td>
</tr>
</tbody>
</table>

5.2.3 SURVIVAL ACCORDING TO eGFR SLOPE

Of the 319 patients, a total of 214 (67%) died during the 10 years of follow-up. The median survival time for the whole cohort was 5.6 (95% CI 4.2-7.0) years. Cause of death was cardiovascular in 44% and infection in 22% of all patients, with no significant difference between eGFR tertiles.

The risk of death did not significantly differ between patient groups in unadjusted analysis (Table 8). When adjusted for age and gender, however, the RR of death for the group with the fastest eGFR decline was 1.73 compared to the slowest eGFR decline group (Table 8 and Figure 4). With additional adjustment either separately or in combination for variables that were significantly differently distributed between the tertiles (body mass index, serum albumin, hemoglobin, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, ESRD diagnosis, and comorbidities as a group, and length of nephrological follow-up), the risk of death in all cases diminished (Table 8).
Table 8  Crude and adjusted relative risk (RR) of death according to estimated glomerular filtration rate (eGFR) decline rate during the year before starting chronic renal replacement therapy.

<table>
<thead>
<tr>
<th>eGFR decline rate tertiles (mL/min/1.73 m² per year) (n)</th>
<th>Unadjusted RR (95% CI)</th>
<th>Adjusteda RR (95% CI)</th>
<th>Adjustedb RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slowest (105) (reference group)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate (107)</td>
<td>0.75 (0.54-1.04)</td>
<td>1.09 (0.77-1.52)</td>
<td>0.84 (0.57-1.25)</td>
</tr>
<tr>
<td>Fastest (107)</td>
<td>0.96 (0.69-1.32)</td>
<td>1.73 (1.23-2.44)</td>
<td>1.20 (0.79-1.80)</td>
</tr>
</tbody>
</table>

CI, confidence interval

eGFR decline rate tertiles (mL/min/1.73 m²/year): slowest = less than 3.4, intermediate = 3.4-8.5, fastest = over 8.5.

aAdjusted for age at start of RRT and for gender.

bAdjusted for the 12 variables of the large Cox regression model: age at start of RRT, gender, ESRD diagnosis (compared to glomerulonephritis), comorbidities (all separately: angina pectoris, myocardial infarction, cerebral infarction, left ventricular hypertrophy, cancer), use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, body mass index (per 5 kg/m² increment), blood hemoglobin (per 10 g/L increment), and serum albumin (per 5 g/L increment).

Figure 4  Probability of survival according to tertile of estimated glomerular filtration rate (eGFR) decline rate during pre-dialysis phase. eGFR adjusted for age and gender and expressed in mL/min/1.73 m²/year.

(Reproduced and adapted from Mikko Haapio et al. Decline in Glomerular Filtration Rate During Pre-dialysis Phase and Survival on Chronic Renal Replacement Therapy. Nephrology Dialysis Transplantation (2012) 27 (3): 1157-1163. By permission of Oxford University Press on behalf of ERA-EDTA.)
In order to further explore the factors associated with fast eGFR decline and higher risk of mortality, we constructed a large multivariable model comprising 12 variables in addition to eGFR tertiles (Table 8, farthest right). Judged by data availability, we included 294 patients (92%) of the total cohort, of which 198 (67%) died during follow-up. In this model, age at start of RRT, the comorbidities of cancer and myocardial infarction, serum albumin, and ESRD diagnosis remained statistically significant predictors of survival. Type 1 diabetes and amyloidosis were associated with the worst survival of all ESRD diagnoses analyzed. Decline rate of eGFR in the large model was not a statistically significant predictor of mortality.

5.3 MODALITY OF CHRONIC RENAL REPLACEMENT THERAPY AND SURVIVAL

5.3.1 FACTORS ASSOCIATED WITH DIALYSIS MODALITIES

Results of the primary analysis method, intention-to-treat, showed significant differences in baseline characteristics between those patients who started chronic RRT with HD and those who started with PD (Table 9). The HD patients were on average older, with more commonly anemia and low serum albumin. Regarding ESRD diagnoses, HD patients were less likely to have glomerulonephritis or type 1 diabetes, and more likely to have polycystic disease, type 2 diabetes, or amyloidosis.

A significantly larger proportion of PD patients were placed on the kidney transplant waitlist both at three months and at one year from start of chronic RRT, and underwent significantly more kidney transplantations within two years (Table 10).

In terms of comorbid illnesses, those patients starting on HD modalities were much more likely to have ischemic heart disease, left ventricular hypertrophy, heart failure, peripheral vascular disease, stroke, or cancer than were those starting on PD modalities, and furthermore, HD patients were more likely to present with four or more comorbidities, whereas PD patients were more likely to be free of major comorbidities (Table 11).
Table 9  Patient characteristics according to dialysis modality group in Study III.

<table>
<thead>
<tr>
<th></th>
<th>HD</th>
<th>PD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>3,246</td>
<td>1,217</td>
<td>–</td>
</tr>
<tr>
<td>Males, %</td>
<td>63.6</td>
<td>64.3</td>
<td>0.217</td>
</tr>
<tr>
<td>Age at RRT start, years median (IQR)</td>
<td>64.4 (53.9-73.2)</td>
<td>55.2 (43.1-66.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body mass index, median (IQR)</td>
<td>26 (23-30)</td>
<td>25 (22-28)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>eGFR (MDRD) at RRT start, ml/min/1.73 m² median (IQR)</td>
<td>8.5 (6.5-11.2)</td>
<td>8.8 (6.7-11.2)</td>
<td>0.195</td>
</tr>
<tr>
<td>Hemoglobin, g/L, median (IQR)</td>
<td>105 (95-116)</td>
<td>114 (104-123)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Albumin, g/L, median (IQR)</td>
<td>33 (28-37)</td>
<td>35 (30-38)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ESRD dg, % within modality group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>12.7</td>
<td>17.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Polycystic disease</td>
<td>10.2</td>
<td>6.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>10.1</td>
<td>29.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>22.7</td>
<td>14.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>3.6</td>
<td>4.0</td>
<td>0.540</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>5.0</td>
<td>2.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Nephrosclerosis</td>
<td>5.9</td>
<td>5.3</td>
<td>0.445</td>
</tr>
<tr>
<td>Other</td>
<td>14.1</td>
<td>10.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Unknown</td>
<td>15.7</td>
<td>11.1</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

HD, hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy; IQR, interquartile range; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease formula; ESRD, end-stage renal disease


Table 10  Kidney transplant waitlist status and transplantations according to dialysis modality group (percent within modality group).

<table>
<thead>
<tr>
<th></th>
<th>HD</th>
<th>PD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>On transplant waitlist at three months from RRT start</td>
<td>3.9</td>
<td>13.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>On transplant waitlist by one year from RRT start</td>
<td>22.8</td>
<td>50.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Kidney transplantation within two years from RRT start</td>
<td>13.7</td>
<td>28.1</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

HD, hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy
<table>
<thead>
<tr>
<th>Type of comorbidity</th>
<th>HD</th>
<th>PD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina pectoris</td>
<td>23.2</td>
<td>14.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>16.6</td>
<td>13.2</td>
<td>0.006</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>35.7</td>
<td>29.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>11.9</td>
<td>7.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>14.4</td>
<td>8.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease with surgery</td>
<td>8.5</td>
<td>4.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease with limb amputation</td>
<td>5.0</td>
<td>3.3</td>
<td>0.018</td>
</tr>
<tr>
<td>Stroke</td>
<td>12.3</td>
<td>9.7</td>
<td>0.022</td>
</tr>
<tr>
<td>Cancer</td>
<td>12.8</td>
<td>5.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Number of comorbidities</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>None</td>
<td>46.3</td>
<td>56.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>One</td>
<td>24.3</td>
<td>23.7</td>
<td>0.671</td>
</tr>
<tr>
<td>Two</td>
<td>12.1</td>
<td>10.4</td>
<td>0.115</td>
</tr>
<tr>
<td>Three</td>
<td>8.3</td>
<td>5.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Four or more</td>
<td>8.9</td>
<td>4.5</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

HD, hemodialysis; PD, peritoneal dialysis


5.3.2 DIALYSIS MODALITY AND SURVIVAL

Of the total 4,463, 1,887 (42%) died during the 10 years of follow-up, with a median survival of 5.2 (95% CI 4.9-5.6) years. A significant survival advantage on PD emerged (median 8.1 [95% CI 6.8-9.4] years on PD vs. 4.7 [95% CI 4.5-5.0] years on HD).

5.3.2.1 Intention-to-treat analysis

The primary analysis method was intention-to-treat. Unadjusted analysis showed a significantly lower risk of death for those patients who started on PD (RR 0.65, 95% CI 0.58-0.73, p<0.001) (Table 12). However, after adjusting for age and gender, no significant survival difference emerged. To perform comprehensive control of confounders, we used a large multivariable model with 26 variables. Of all the 3,939 patients in the model (88% of the total cohort), 1,619 (41%) died during follow-up. Contradicting the unadjusted model, this model showed no statistically significant difference in RR of death between the patients on the two dialysis modalities. Censoring or not censoring at the time of kidney transplantation did not alter these results, nor did adjustment for transplantation as a time-dependent variable (data not shown), which resulted in a very similar
outcome as with censoring at transplantation. Figure 5 portrays unadjusted and multi-adjusted survival probabilities of the intention-to-treat analysis (Figure 5).

We tested the proportional hazards assumption for HD versus PD and found that it was not violated in the Cox model (p=0.254).

Table 12 Relative risk (RR) of death with the primary and the secondary analysis techniques and according to the chronic dialysis modality group.

<table>
<thead>
<tr>
<th>Intention-to-treat analysis (n)</th>
<th>Unadjusted RR (95% CI)</th>
<th>Adjusted(^a) RR (95% CI)</th>
<th>Adjusted(^b) RR (95% CI)</th>
<th>Adjusted(^c) RR (95% CI)</th>
<th>Censored at Tx(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD(^d) (3246)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PD (1217)</td>
<td>0.65 (0.58-0.73)(^a)</td>
<td>0.90 (0.80-1.01)</td>
<td>1.07 (0.94-1.22)</td>
<td>1.04 (0.91-1.19)</td>
<td>1.09 (0.95-1.25)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>As-treated analysis (n)</th>
<th>Unadjusted RR (95% CI)</th>
<th>Adjusted(^a) RR (95% CI)</th>
<th>Adjusted(^b) RR (95% CI)</th>
<th>Adjusted(^c) RR (95% CI)</th>
<th>Censored at Tx(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD permanently(^d) (3064)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PD permanently (885)</td>
<td>0.62 (0.54-0.70)(^a)</td>
<td>0.95 (0.83-1.09)</td>
<td>1.17 (1.00-1.37)(^f)</td>
<td>1.12 (0.96-1.31)</td>
<td>1.33 (1.12-1.56)</td>
</tr>
<tr>
<td>HD to PD (182)</td>
<td>0.99 (0.79-1.23)(^e)</td>
<td>1.32 (1.06-1.65)(^f)</td>
<td>1.23 (0.97-1.57)</td>
<td>1.25 (0.98-1.59)</td>
<td>1.11 (0.87-1.42)</td>
</tr>
<tr>
<td>PD to HD (332)</td>
<td>0.73 (0.61-0.87)(^e)</td>
<td>0.85 (0.71-1.02)</td>
<td>0.96 (0.78-1.17)</td>
<td>0.96 (0.79-1.18)</td>
<td>0.85 (0.69-1.04)</td>
</tr>
</tbody>
</table>

CI, confidence interval; Tx, kidney transplantation; HD, hemodialysis; PD, peritoneal dialysis

\(^a\)Adjusted for age at start of RRT and for gender.

\(^b\)Adjusted for the 26 variables of the large Cox regression model: age at the start of RRT, gender, transplant waitlist status at three months from RRT start, body mass index, end-stage renal disease diagnosis, RRT start year, eGFR at RRT start, serum urea, serum albumin, blood hemoglobin, systolic blood pressure, diastolic blood pressure, use of vitamin D, use of erythropoietin, and comorbidities (angina pectoris, myocardial infarction, cardiac left ventricular hypertrophy, heart failure, peripheral vascular disease, surgery for peripheral vascular disease, limb amputation for peripheral vascular disease, stroke and cancer), medication or diet treatment for hyperlipidemia, medication for hypertension, and cigarette-smoking status.

\(^c\)Adjusted as previously, but omitting the variable “transplant waitlist status at three months from RRT start”.

\(^d\)Reference group

\(^e\)ps0.001

\(^f\)p<0.05

5.3.2.2 As-treated analysis

We used as-treated analysis as a secondary approach. In line with the results of the primary analyses, it also indicated the lowest unadjusted risk of death for patients who started with PD (Table 12). Again similarly as for primary analyses, adding adjustment for age and for gender reduced survival differences mostly to a nonsignificant level. However, employing the large multivariable model resulted in a 17% (p=0.047) higher mortality risk for patients exclusively treated with PD, and even further increased RR (33%, p≤0.001) when censoring at transplantation in the same patient group. Figure 6 illustrates both unadjusted and fully adjusted survival probabilities of the as-treated analysis (Figure 6).

Between those exclusively either on PD or on HD, no nonproportionality in the hazards appeared observable over time (p=0.887), but the hazards of those who switched from PD to HD or from HD to PD were not proportional to the hazards of those who were exclusively treated by HD (p=0.003 and p=0.005, respectively).
5.3.2.3 Subgroup analyses

To investigate whether the association between dialysis modality and survival differed between patient subgroups, we assessed interactions between treatment modalities and other explanatory variables; employing our multivariable model, we found no significant interactions. Of note, no interaction occurred between treatment modality and time spent on RRT (p=0.857). A tendency arose towards lower mortality in PD patients under age 45 and higher mortality in PD patients over age 75 compared to those of HD patients. PD patients with amyloidosis also showed a tendency toward higher mortality.

5.4 ONE- AND TWO-YEAR MORTALITY PREDICTION FOR PATIENTS STARTING CHRONIC DIALYSIS

The two patient cohorts under investigation, the training and validation groups, differed significantly with respect to patient age at RRT start and body mass index, both of which were higher in the validation group. The validation group included more males, and more frequently the comorbidities angina pectoris, left ventricular hypertrophy, and cancer. A shift also occurred in the distribution of ESRD diagnoses toward fewer cases of pyelonephritis and amyloidosis and more
cases of nephrosclerosis from the older training group to the newer validation group.

A clear and somewhat unexpected finding was the significantly lower mortality rate of the validation group (Table 13).

### Table 13  Mortality according to patient group in Study IV.

<table>
<thead>
<tr>
<th></th>
<th>Training group (n=4,335)</th>
<th>Validation group (n=1,768)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>During one year</td>
<td>During two years</td>
</tr>
<tr>
<td>Mortality, all patients, n (%)</td>
<td>597 (13.8)</td>
<td>1,080 (24.9)</td>
</tr>
</tbody>
</table>

### 5.4.1 PREDICTORS OF MORTALITY

We first tested the effect on death risk of 32 variables. Including all the variables in the logistic regression model resulted in 15 (one-year model) and 13 (two-year model) variables with p-values less than 0.05. We then compared the predictive performance of these variables in several combinations and finally chose, based on results from calibration and discrimination, seven variables to the final one-year model and six variables to the final two-year model. In the logistic regression model, all of these variables were highly significant (p-value less than 0.001) (Table 14).

We found three significant first-degree interactions in the one-year model: between ESRD diagnosis and age at start of RRT, between serum albumin and age at start of RRT, and between ESRD diagnosis and heart failure, and one interaction in the two-year model: between ESRD diagnosis and heart failure.
Table 14  Variables of the final mortality prediction models (with multivariable odds ratios and 95% confidence intervals).

<table>
<thead>
<tr>
<th>Variables of the models</th>
<th>One-year model</th>
<th>Two-year model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at RRT start, years</td>
<td>1.05 (1.04-1.06)</td>
<td>1.06 (1.05-1.06)</td>
</tr>
<tr>
<td>ESRD diagnosis</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Polycystic disease</td>
<td>0.56 (0.28-1.11)</td>
<td>0.73 (0.46-1.17)</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>2.16 (1.37-3.39)</td>
<td>2.81 (1.98-3.99)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>1.63 (1.13-2.36)</td>
<td>2.17 (1.62-2.90)</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>1.14 (0.60-2.19)</td>
<td>0.79 (0.46-1.38)</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>3.10 (1.98-4.87)</td>
<td>3.72 (2.54-5.43)</td>
</tr>
<tr>
<td>Nephrosclerosis</td>
<td>1.48 (0.91-2.40)</td>
<td>1.62 (1.10-2.40)</td>
</tr>
<tr>
<td>Other</td>
<td>2.38 (1.63-3.49)</td>
<td>2.32 (1.70-3.17)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1.49 (1.00-2.20)</td>
<td>1.51 (1.10-2.07)</td>
</tr>
<tr>
<td>Serum albumin, g/L</td>
<td>0.96 (0.95-0.97)</td>
<td>0.96 (0.94-0.97)</td>
</tr>
<tr>
<td>Serum C-reactive protein, log</td>
<td>1.16 (1.07-1.24)</td>
<td>1.11 (1.05-1.18)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.10 (1.65-2.69)</td>
<td>2.48 (1.98-3.10)</td>
</tr>
<tr>
<td>Serum phosphorus, mmol/L</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>less than 1.53</td>
<td>1 (reference)</td>
<td>–</td>
</tr>
<tr>
<td>1.53 - &lt; 2.0</td>
<td>0.75 (0.59-0.97)</td>
<td>–</td>
</tr>
<tr>
<td>2.0 or higher</td>
<td>1.15 (0.92-1.45)</td>
<td>–</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.66 (1.30-2.11)</td>
<td>–</td>
</tr>
<tr>
<td>Peripheral vascular disease with limb amputation</td>
<td>–</td>
<td>1.90 (1.36-2.65)</td>
</tr>
</tbody>
</table>

RRT, renal replacement therapy; ESRD, end-stage renal disease

5.4.2 VALIDATION OF THE MODELS

After construction of the two final models, we tested their predictive performance in the validation group (Table 15). Compared to the training group and using the c-statistic (area under the curve, AUC), predictive ability was equal in the validation group in the one-year model and somewhat lower in the two-year model. To assess calibration of the models we categorized predicted probabilities of death into deciles and compared average predicted probabilities to mortality observed among the deciles (Figure 7). This resulted in less than optimal calibration in both models, with overestimation of death risks which was also indicated by the significant p-values in the Hosmer-Lemeshow test. Thus, the actual mortality in the validation group was lower than predicted by both the one- (Figure 7, left) and two-year (Figure 7, right) models.
Table 15 Predictive performance of final models.

<table>
<thead>
<tr>
<th>Model</th>
<th>Training group (4,335)</th>
<th>Validation group (1,768)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>One-year</td>
<td>Two-year</td>
</tr>
<tr>
<td>n</td>
<td>4,335</td>
<td>4,335</td>
</tr>
<tr>
<td>AUC</td>
<td>0.768</td>
<td>0.764</td>
</tr>
<tr>
<td>Hosmer-Lemeshow test p-value</td>
<td>0.018</td>
<td>0.069</td>
</tr>
</tbody>
</table>

AUC, area under the curve

*those for whom data on all variables included were available

Figure 7 Calibration of the one-year model (left) and two-year model (right). Average predicted probabilities of death (mean, blue bars) and observed mortality (proportion of patients who died, orange bars) according to decile of predicted probability of death (y-axis).
6 DISCUSSION

6.1 FACTORS ASSOCIATED WITH SURVIVAL OF PATIENTS ON CHRONIC RRT

6.1.1 PATIENTS WITH TYPE 1 DIABETES ON CHRONIC RRT AND SURVIVAL

In Study I, we showed that survival of patients with type 1 diabetes receiving RRT has significantly improved. For patients beginning RRT in 2000–2005, risk of death was 77% lower than for those entering RRT during 1980–1984. This study to our knowledge was the first to observe improvement in prognosis of patients with type 1 diabetes on chronic RRT with a follow-up lasting up to 28 years.

Our observations are in concordance with those of Sørensen and colleagues, who found improved overall survival of patients with diabetes (type 1 and 2 combined) by 14 to 18% between each five-year period and the one following in 1990–2005 (21). Our findings are also in line with the observations of van Dijk and colleagues in their European study including 10 countries. Their patients with type 1 diabetes were increasingly older at RRT start over the period 1991–1999 (20). Albeit having had a modest (adjusted) two-year mortality reduction, their five-year crude survival was only 24% for those having no a kidney transplant. Mortality reduction was more pronounced in those with a transplant, with 79% survival at five years.

In contrast to our results, a registry study by Villar and colleagues from Australia / New Zealand showed no progress in survival estimate during 1991–2005, even for those patients with type 1 diabetes with a kidney transplant (22). No obvious explanation existed for the dissimilarity with our results, but it may be linked to the much lower incidence of RRT resulting from type 1 diabetes in Australia / New Zealand.

Our observation includes several important aspects. First, a continuous and progressive increase has occurred in median survival time of patients with type 1 diabetes on RRT, exceeding eight years for those entering RRT in 2000–2005. Second, the probability of survival on RRT has increased in all age-groups. Third, this improvement in survival has taken place despite the increasing age of patients starting RRT and the decreasing proportion of patients with kidney transplantation. Fourth, the survival prognosis of patients with type 1 diabetes has improved significantly more than that of patients with glomerulonephritis.

It should also be noted that many favorable processes related to management of type 1 diabetes and chronic RRT have developed during recent decades. Treatment of type 1 diabetes has made many remarkable leaps forward since
the 1970s. Improved insulin regimens and equipment enabling more intensive blood glucose monitoring have been crucial in making treatment of type 1 diabetes easier and safer. In addition, many efforts to better manage chronic dialysis therapy, in terms of quality, dose, and flexibility in delivery, have succeeded. Examples have been modern synthetic high-flux hemodialyzers with better toxin clearance and biocompatibility as well as use of ultrapure fluid in on-line HDF (108, 162). Similarly, reducing the symptoms and the consequences of uremia and enhancing patient autonomy are PD fluids with better biocompatibility and maximized ultrafiltration, and overnight automated PD (115, 119). All this progress may also have contributed to better patient survival, but such evidence is still inadequate (51, 163-165).

Patients with type 1 diabetes live longer on chronic RRT. Clear proof is that despite a declining relative incidence of patients with type 1 diabetes entering chronic RRT, their proportion of all ESRD patients has remained constant (1). As our study results indicate, this may in part result from developments in diabetes care, because in the reference cohort (glomerulonephritis patients), survival improvement was less. It is also possible that management of cardiovascular risk factors, the leading causes of death in patients with type 1 diabetes, may be better achieved in these patients. Importantly though, most of the improvement in prognosis of patients with type 1 diabetes seems attributable to progress in RRT.

6.1.2 PRE-DIALYSIS PHASE eGFR DECLINE RATE AND SURVIVAL

In Study II, we investigated association of the eGFR decline pattern during one year before start of chronic RRT with subsequent survival on RRT. The rate of eGFR decline emerged as a factor that correlated with survival, not as a causal factor, but rather as a marker of a group of confounding factors. Our study was the first published in the field to investigate eGFR decline and the resultant survival on RRT.

Our results are in accordance with those of Rifkin and colleagues, Wu and colleagues and Chen and colleagues (95-97). These studies focused, however, either on mild renal insufficiency or only on the predialysis phase and did not reach to the start of dialysis. In the study by Rifkin and colleagues, an annual eGFR decline over 3 ml/min/1.73 m² was associated with increased cardiovascular and all-cause mortality (95). Wu and colleagues found an association between intense predialysis patient education and a slower eGFR decline (slight increase vs. -1.3 ml/min/1.73 m² during 12 months, test vs. control group, respectively), a lower risk for developing ESRD, and a lower risk of all-cause death (96). Chen and colleagues found late nephrology referral to correlate with faster eGFR decline (1.06 vs. 0.57 mL/min/1.73 m²/month) and higher mortality (97).
In our study, eGFR decline more than 8.5 ml/min/1.73 m² during the year preceding RRT start was associated with increased risk of death. We also found that patients with different causes of ESRD had different rates of eGFR decline. For instance, many of the patients with type 1 diabetes had a faster decline than did many of those with pyelonephritis or polycystic disease. Consequently, of all ESRD diagnoses in our study, type 1 diabetes and amyloidosis were associated with the worst survival, clearly worse than that in diagnoses of primary renal disease. The worse outcome associated with these ESRD causes is already known (22, 166). ESRD diagnosis, however, explains only a small part of the mortality effect of eGFR in our study, because when we adjusted for ESRD diagnosis, the association between decline and mortality weakened only slightly.

To clarify the potential causal as well as confounding factors behind survival rates in the three eGFR groups, we performed multivariable adjustment. The more comprehensive the adjustment, the weaker the association between eGFR decline and survival (finally becoming nonsignificant). This is an indication of multiple confounding factors correlating with both eGFR and mortality risk. Analyzing these factors one by one, we found especially ESRD diagnosis, serum albumin, and comorbidities to weaken the association between tertiles of eGFR decline and mortality. In our multivariable model, age at RRT start, cancer, myocardial infarction, serum albumin, and ESRD diagnosis emerged as statistically significant predictors of mortality. These factors to some degree must lie behind the increased mortality risk indicated by the faster eGFR decline.

To further analyze the factors affecting survival on RRT we investigated the effect of kidney transplantation, causes of death, and length of nephrological follow-up. Interestingly, kidney transplantation was equally frequent between eGFR decline tertiles, as were causes of death. Nephrological follow-up, however, was shorter for the fast eGFR decliners, which could indicate a disadvantage from the short follow-up, but was most probably explainable by the more rapidly deteriorating renal function that brought the patients to nephrology referral later.

Low serum albumin was for us an independent predictor of rapid eGFR decline. Hypoalbuminemia is a well-known prognostic factor, portending adverse outcome in ESRD patients (58). It is generally a marker of poor nutritional status, chronic infection or inflammation, and sometimes of a severe nephrological disease with high proteinuria (167, 168). All these causes of hypoalbuminemia are also linked to worse outcome; logically low serum albumin could thus partly explain the faster eGFR decline associated with it among our study patients. Furthermore, although we had no data on frequency and magnitude of proteinuria, we may presume that proteinuria was present in many of the patients with low serum albumin. The association of proteinuria with worsening CKD and with cardiovascular adverse events in renal patients is established (169).
Measurement of eGFR is widely spread in the follow-up of patients approaching the start of chronic RRT. However, based on present knowledge, knowing whether eGFR is high or low at RRT start does not reliably help predict survival of patients on RRT, nor do we know the optimal timing of RRT start with respect to eGFR and the ensuing survival on RRT. The formulae most commonly used for estimation of GFR, the Cockcroft-Gault, MDRD, and at present, CKD-EPI, are not optimal, with some investigators questioning their reliability (77, 170, 171). However, compared to serum creatinine measurement alone, the eGFR formulae considerably increase accuracy of renal function assessment in chronic and moderate or more severe insufficiency (25). The eGFR formulae are also inexpensive and readily available in a clinical setting. Thus, despite the well-recognized problems associated with serum creatinine-based estimation of GFR (e.g., abnormal muscle mass or poor nutritional status), these formulae are at present the most favored in follow-up of predialysis patients (77, 81). We saw it as important therefore to explore the predictive abilities of an eGFR formula for patients starting chronic RRT.

6.1.3 DIALYSIS MODALITY AND SURVIVAL

In Study III, we compared survival of patients on chronic RRT according to dialysis modality on day 91 after RRT start, and found a significantly lower mortality risk for PD patients than for HD patients. However, this finding only appeared in unadjusted analyses, because in our primary analyses (the intention-to-treat approach) with comprehensive adjustment for confounding factors, no significant mortality risk difference emerged. Interestingly, in our secondary analyses (the as-treated method) with full adjustment, those exclusively treated with PD had a 17 to 33% higher risk of death than did those exclusively treated with HD.

The results of the primary and secondary analysis methods turned out to differ somewhat. We chose the intention-to-treat approach as our primary method for pragmatic reasons, since in reality it is infrequently known at the time of chronic RRT start whether a patient will later change dialysis modality. In addition, in the as-treated method, results would be subject to selection bias, because for a patient to be included in a group of modality changers, he/she must have lived until the modality switch. On the other hand, the secondary method (as-treated) can offer additional and versatile information not offered by the intention-to-treat method, and also enables direct comparison of those patients treated only with PD to those treated only with HD.

In observational studies like ours, comparing outcome (survival) can be complex because the groups compared against each other are dissimilar with regard to many variables affecting survival (61, 137). These factors are thus confounders, but with known confounders, the problem in comparisons can be solved by statistical adjustment. All this requires that reliable data are available.
Nevertheless, unknown confounders may still exist. Being on a transplant waitlist was clearly more frequent among PD patients and strongly correlated with survival, thus manifesting as a strong confounder. Whether a patient is waitlisted serves as a proxy of many favorable characteristics; survival analyses should therefore be adjusted for this factor. For this reason, we added adjustment for kidney transplant waitlist status at three months from RRT start at the head of all the other variables for which adjustment was done. Although waitlist status at one year could have been an even stronger confounder, and adjusting for it would probably have made our model even more comprehensive, we chose waitlist status at three months, as this was the time-point at which dialysis modalities were registered and because these data were already available at start of follow-up. Moreover, it could have carried with it a survivor effect.

As an alternative analysis, we performed censoring at time of kidney transplantation, assuming (in Kaplan-Meier and Cox regression) that the probability of survival of the censored transplanted patients would be same as that of those who remained in the follow-up. Censoring at transplantation could theoretically allow us to account for differences in transplantation rates between dialysis modalities. But, as we know that transplanted patients present with many favorable prognostic characteristics and that transplantation in itself may improve prognosis, this assumption of equal survival probability is not really true. With censoring at transplantation, no change was evident in our primary analyses, but instead we saw a further increased mortality risk for PD patients in the secondary analyses (Table 12). This evidently resulted from the higher number of transplanted patients belonging to the group treated only by PD. Additionally, instead of censoring at transplantation, we adjusted for transplantation as a time-dependent variable (data not shown), and produced results very similar as when censoring at transplantation. However, the same applies to both these actions: censoring at transplantation and adjusting for transplantation as applies to adjusting for transplant waitlist status at one year; those data did not exist at the start of follow-up, and we therefore decided to use waitlist status at RRT start.

In many studies, investigators explored interactions between survival during different dialysis modalities and between patient subgroups. Some results have been conflicting. In some studies, PD has been associated with better survival in younger patients without comorbidities (39, 40) and with worse outcome in older diabetic patients (41, 47). Conversely, no difference appeared in two registry studies, one comparing survival of non-diabetic CAPD and HD patients (46), and the other comparing initial dialysis modalities of non-diabetic waitlisted patients (56). Our study, however, showed no significant interactions between dialysis modality and age-group or comorbidities with respect to survival. It did, however, show a tendency towards better survival in young and worse survival in old patients on PD, a finding which might have been significant had we had more patients.
To date, only one study has used randomized patient selection in comparing dialysis modalities with respect to survival (156). Regrettably, that study was prematurely halted because of its low inclusion rate, and thus did not reach sufficient statistical power. Although our study was observational and not randomized, we were able to use exceptionally comprehensive data in terms of national and patient coverage as well as information on potential confounders. Moreover, when deciding which dialysis modality is best for a given patient, all factors affecting it from the patient’s social and work status and physical and cognitive condition to the variety of nephrological resources, it seems that no large randomized study in the field is feasible. Therefore, well-conducted observational studies, which hopefully provide relevant and useful information for management of ESRD populations, are justified.

6.1.4 PREDICTIVE MODELS FOR SURVIVAL ESTIMATION

In Study IV, we developed two mortality prediction algorithms for one- and two-year mortality estimation for patients starting chronic dialysis.

Life-long treatment, chronic RRT, is strenuous and demanding not only for the individual patient but also for the health-care system. Models for estimation of mortality risk may serve both nephrologists and their ESRD patients, as well as the nephrological health-care system as a whole. First, a baseline risk-stratification could help to identify patients at increased risk, enabling possible preventive measures. In outpatient management of patients who gradually approach the start of chronic RRT, such identification could possibly sharpen individualized patient care and hopefully delay the start of chronic RRT. Second, prognostic models could give an overview beyond usual patient-level considerations in reaching the best treatment decisions on, for instance, level of treatment activity, choice of dialysis modality, and the choice to proceed to kidney transplantation or not. Arguably, in many cases, clinical experience and expertise will suffice for a rough estimation of mortality risk, but at the same time prognosis provided by models could offer the patient some justification for decisions concerning his treatment. Third, management of expanding ESRD populations will require rational use of limited nephrological resources, in which survival prediction models could help in identifying patients who will benefit the most from nephrological interventions. Fourth, in efforts to reach equal and fair sharing of limited resources, models could help in making critical comparisons between practice patterns and outcome of patients in differing nephrological units. Fifth, to be able to compare scientific work on varied ESRD populations, it is important to have reliable baseline risk estimation. Prediction models could assist in this, and also in selection of study populations.
For these reasons, mortality prediction models have been developed for patients entering chronic dialysis. Our models focused on survival during the first two years after patients entered dialysis. We used a separate, less recent cohort for construction of the models, and then validated the models with an external, more recent patient cohort. The models showed comparably good predictive ability, especially for the first year on RRT, and somewhat weaker ability for the first two years on RRT. The latter resulted from the significantly lower mortality of the validation group, which distorted calibration of the models and overestimated risk of death. It is important, though, that we chose a more recent and external patient cohort for validation, because this realistically reflects how predictive models are applied: to future patients. In contrast to our study, in most (almost all) earlier studies, validation cohorts were randomly drawn from the entire study population (62-65, 67-70), resulting in more uniform testing and validation groups, and therefore also, in many cases, good discrimination ability. However, although our approach slightly reduced the accuracy of our models, we see it as necessary for reliable validation.

Many similarities also arise between other studies in the field and ours, for instance, outcome with respect to discrimination ability, and the statistical methods used. An AUC for mortality prediction of 0.72 to 0.84 for the first year on RRT and 0.67 to 0.75 for the first two years on RRT has been common, and an AUC of 0.75 has usually been considered reasonably good (64, 66-70, 159, 160). Our results match well with these findings and requirements. The statistical method mostly employed in survival studies aiming at building prognostication models has been multivariable logistic regression analysis, typically using stepwise selection of variables, and also in our study. Another similarity between other studies is data source, which usually has been a health-care registry or administrative database (60-70, 159), deriving information from incident ESRD populations (60, 61, 64, 66-69).

Our results may be lined up against others’ results also with regard to the era of patient inclusion and patient characteristics potentially affecting survival outcome. Our training cohort started RRT during 2000–2008 and was thus from approximately the same years as cohorts of other studies referenced here (64-70, 159, 160). Our validation cohort, however, from the year 2009 onwards, is clearly the most contemporary one thus far, with our follow-up lasting until the end of 2013. This may add reliability and credibility to our study results. Unexpectedly, mortality had significantly decreased in our newer cohort, although many patient characteristics had evolved to some degree in an unfavorable direction considering how these factors may affect survival. For instance, age at RRT start and proportion of males had increased, as well as numbers with cancer. Serum albumin was lower in the newer cohort, a factor known to worsen prognosis strongly. Patients of the validation group were also more anemic and had higher serum phosphorus,
although these differences seemed small judged by experience in clinical work. On the other hand, patients of the newer cohort had a higher body mass index and serum creatinine, both factors generally linked to improvement of prognosis. Of other patient-level factors present in studies worth mentioning are the quite similar ages at RRT start as well as the proportion of patients starting with PD treatment (64, 67, 68). AUCs for survival on RRT reached in those studies: 0.72-0.78, have also been close to the ones we detected.

Although the performance of many prediction models has been comparatively good, these models have by no means been near to optimal. Many reasons lie behind the limited ability of models to perform exact prognostication. Especially important are the large numbers of patient- and treatment-related factors potentially affecting survival and thus probably confounding survival analyses. Many of these factors are known and can be accounted for in the analyses, but many times the factors are not precisely characterized, or at least their effect on survival is poorly known. Furthermore, many of these factors tend to change over time. For instance, current ESRD patients are older than in the past and present with more comorbidities, thus being at increased risk of death. On the other hand, advancements both in general health care and in nephrological treatment are likely to improve their prognosis. Prognostic models built on earlier data may thus not achieve equal performance in future. Moreover, models are likely to overestimate mortality risk in newer populations when real improvement in prognosis occurs, a fact which became apparent in our study.

6.2 LIMITATIONS AND STRENGTHS

As to limitations, first, due to the population-specific data of the Finnish Registry for Kidney Diseases, our results may not be directly applicable to other populations. For instance, Study I with its clearly improved survival in patients with type 1 diabetes on chronic RRT might not be generalizable to other countries, because the incidence of type 1 diabetes is among the highest in the world in Finland, with much attention paid to treating these patients. Similarly, with the results of Study IV, because the mortality prediction models for ESRD patients were based on data of only Finnish patients, the models may not perform equally well for others than Finns.

Second is the question of whether to do censoring at a certain point of follow-up. In survival studies of ESRD patients, kidney transplantation may be especially important. In Study I, the number of patients receiving a kidney transplant was lower among those with type 1 diabetes than for glomerulonephritis patients (45% vs. 50%), and thus, had we performed censoring at transplantation, this would have further worsened the survival estimate of glomerulonephritis patients.
compared to diabetes patients. To account for this difference we adjusted for having or not having received a transplant within the first two years on RRT (Table 4). In Study II, no difference appeared in the frequency of kidney transplantation between the eGFR decline tertiles; we therefore neither censored at the time of transplantation nor adjusted for it. In Study III, we chose to present results both with and without censoring at time of transplantation. As was obvious in that study, censoring at transplantation affected the results to favor HD over PD in survival comparisons (i.e., increasing RR of death in PD compared to HD) (Table 12), because substantially more PD patients received a transplant during the follow-up (Table 10). In addition, data on future transplantations were unavailable when follow-up was started. In the main analyses of Study III, we decided, instead, to adjust for waitlist status, which gives similar information about patient characteristics as transplantation does, but at an earlier stage. In that way, we attempted to ensure adjustment for the selective characteristics of future transplantation patients.

Third is the issue related to censoring at transplantation: whether to perform adjustment for transplantation. Although we know that those ESRD patients who later receive a kidney transplant often present with many favorable characteristics (such as higher serum albumin and fewer comorbidities) associated with increased survival, so that adjusting for them would be necessary, in Study III we decided to mimic reality and not adjust for factors of the future. In other words, factors, even those potentially confounding, if they appear only during follow-up (transplantation), we did not adjust for. Instead, we decided to adjust for transplant waitlist status at start of follow-up.

Fourth, data in Study I on diagnostic kidney biopsies confirming the ESRD diagnosis to be diabetes were incomplete. This is a consequence of the long-common practice of performing no kidney biopsies on patients with type 1 diabetes and CKD if they present with other microvascular complications considered to be caused by diabetes (especially retinopathy). In the control group (patients with glomerulonephritis), the percentage of biopsy confirmations increased over the years and reached 85% in the most recent group (1995–2005).

Fifth, in Study IV, due to a reasonably large amount of data lacking in the training group, we performed multiple imputation for missing data; this may have altered analysis results, but to avoid selection bias from excluding patients with missing data, we felt imputation was necessary and expected it to give more reliable study results (172). Importantly, in the validation group no missing data were imputed.

The Finnish Registry for Kidney Diseases is recognized for its exceptionally high-quality data, and furthermore, comprehensive nationwide coverage of ESRD patients and nephrological units. The data included in the registry come directly from dialysis units and nephrologists treating dialysis and transplantation.
patients. The process of regularly performed data collection is well incorporated in the everyday practice of nephrological units.

When using data of the Registry, results are guaranteed to represent Finnish ESRD patients comprehensively. The Registry is estimated to cover 97 to 99% of all Finnish patients receiving chronic RRT since 1965. Therefore, even in observational studies investigators can have reliable data with only a very few patients excluded (those not consenting the use of their information in the Registry, and these patients are nearly nonexistent). Resulting from the complete coverage of Finnish nephrological units the studies are multi-centered, and due to the process of data collection, also prospective in setting.

Of the individual studies underlying this thesis, the particular strength of Study I was the complete Finnish cohort of patients with type 1 diabetes and the length of follow-up that stretched to 28 years. The study was the first to show improvement in the prognosis of patients with type 1 diabetes on RRT, based on such a long observational period. Study II, although rather small, was at its time of publication the first in the field. Study III may be recognized for its unusually comprehensive adjustments, giving the study results special reliability. In Study IV, data were prospectively collected without exclusion. Importantly, we used an external and newer validation group and so gave the models a realistic performance test that better mimicked everyday clinical situations.
CONCLUSIONS

The ESRD population shows high morbidity and mortality. Severe renal insufficiency requiring the start of chronic RRT is a great burden not only on individual patients, but also on health-care systems as a whole. The prognosis of ESRD patients in general has not improved to the degree anticipated, and factors behind heightened mortality are still insufficiently known. Identification of factors associated with the increased risk of mortality in ESRD patients could reveal potential opportunities to improve survival. This thesis was targeted to investigate and identify factors related to prognosis of ESRD patients entering chronic RRT. The main findings were:

Study I: The survival of patients with type 1 diabetes and ESRD has continuously and significantly improved from 1980 onwards in Finland despite the progressively higher age at the start of chronic RRT. Survival of patients with glomerulonephritis (the control group in Study I) has also improved, but to a lesser extent. The improved outcome of patients with type 1 diabetes may result from both improved dialysis treatment and progress in diabetes care, and emphasizes the importance of comprehensive management of diabetes and other cardiovascular risk factors even in patients on chronic RRT.

Study II: In age-adjusted survival analyses, the rapid decline in estimated GFR during the year preceding start of chronic RRT is a marker of increased mortality on RRT. However, the association appears to be non-causal and mainly explained by the confounding effect of ESRD diagnosis, low serum albumin, and other comorbidities.

Study III: Comparison of survival between various dialysis modalities is hindered by patient selection. Many patient characteristics related to survival differ considerably between dialysis modalities, and thus confound the analysis. When these characteristics, most importantly age and kidney transplant waitlist status, are taken into account and adjusted for in survival analyses, no significant overall difference in survival between HD and PD patients emerges. Furthermore, no significant survival difference appeared between subgroups of patients in either dialysis modality.

Study IV: We identified several factors that are independently and significantly associated with survival of ESRD patients on chronic RRT. Based on these factors, we developed one- and two-year mortality prediction models with comparatively good prognostication ability (AUC 0.77 to 0.74). Due to the convenient size of the models in terms of numbers of variables, they can easily be applied in clinical work, to help nephrologists do individualized treatment-planning, and also to offer ESRD patients insight into decisions concerning treatment.
These studies were carried out from 2008 onwards at the University of Helsinki and in Helsinki University Hospital, Abdominal Center, Nephrology (formerly: Division of Nephrology, Department of Internal Medicine), and the Finnish Registry for Kidney Diseases. I express my gratitude to the chief physicians of these institutions, Professor Per-Henrik Groop, Docent Eero Honkanen, and Professor Emerita Carola Grönhagen-Riska, respectively, for providing the excellent surroundings to perform the studies.

I am especially grateful to Docent Eero Honkanen, Chief Physician in Nephrology. Eero Honkanen took the initiative for me to start research in nephrology and has then most kindly paved the way. Originally the main theme of my thesis was considered to handle acute kidney injury, but rather soon, after an offer I could not refuse (by Docent Patrik Finne), the thesis topic was by mutual agreement converted to focus on the prognosis of patients on chronic renal replacement therapy. Over the years, Eero has shown genuine interest in this thesis and has been most encouraging and supportive towards my research work and arranged opportunities for me to have regular research leaves.

My deepest gratitude goes to my two supervisors, Docent Patrik Finne and Professor Carola Grönhagen-Riska, both of whose brilliance in nephrological epidemiology is admirable. I feel privileged to have had the opportunity to learn from them. Patrik Finne has during the years of these studies given me countless hours of help at every turn of the project, and has not grown tired of teaching me over and over again the research methods and statistical analyses necessary for these studies. At times when completion of this thesis seemed very distant, Patrik showed remarkable faith in the project and in me and patiently helped things go forward. I could not imagine a thesis supervisor more pleasant to work with. I am also greatly indebted to my other supervisor, Professor Carola Grönhagen-Riska, who has provided invaluable advice and support for this thesis. I greatly respect Carola’s clear views and superior ability to guide research projects on a large scale, ensuring that I could concentrate in the most relevant research questions and get the work done.

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