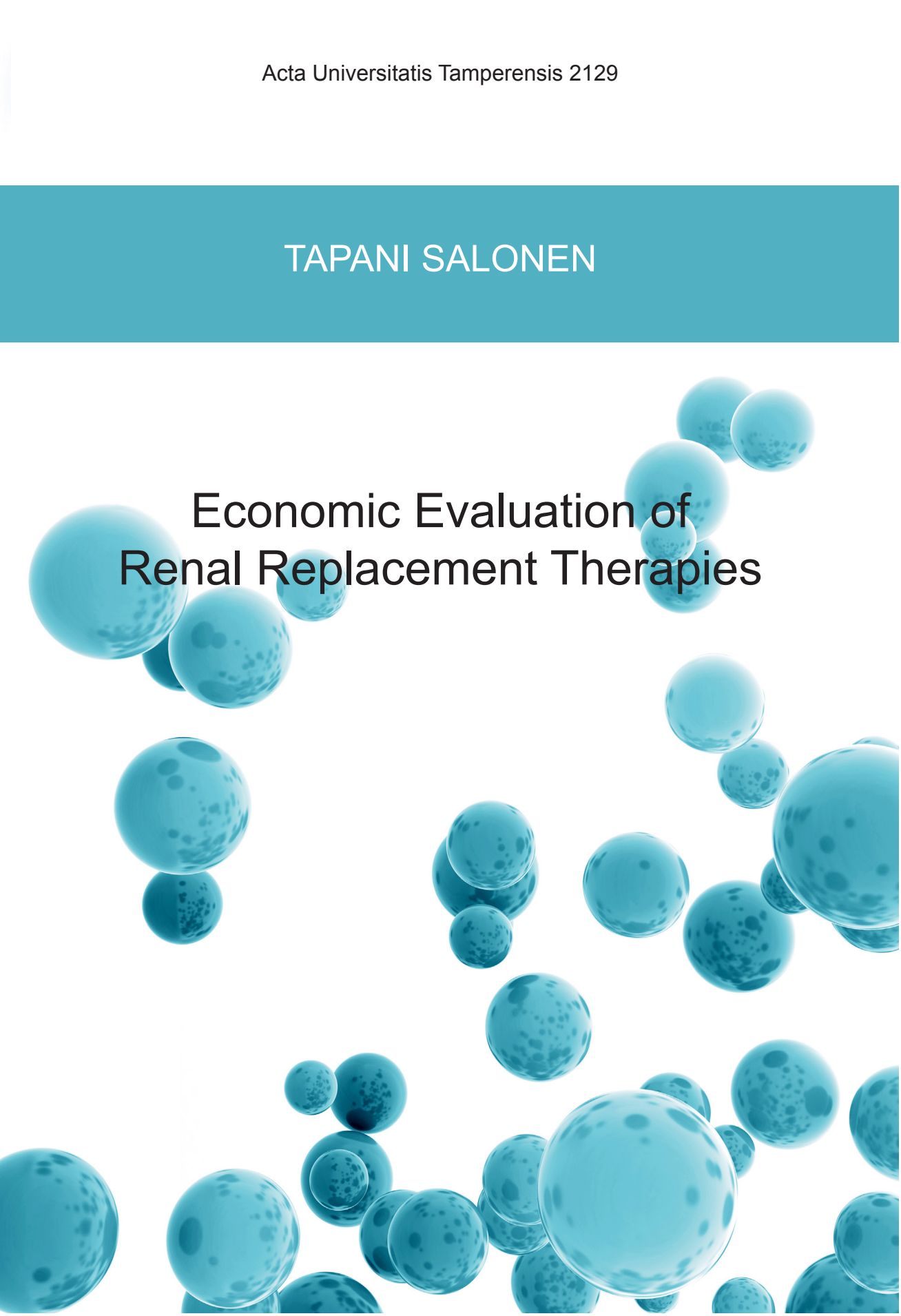


TAPANI SALONEN

Economic Evaluation of Renal Replacement Therapies

The background of the cover is white, featuring a decorative pattern of numerous blue, semi-transparent spheres of varying sizes. These spheres are scattered across the page, with some appearing larger and more prominent than others, creating a sense of depth and movement. The spheres have a subtle texture and are rendered with soft shadows, giving them a three-dimensional appearance.



TAPANI SALONEN

Economic Evaluation of
Renal Replacement Therapies



ACADEMIC DISSERTATION

To be presented, with the permission of
the Board of the School of Medicine of the University of Tampere,
for public discussion in the small auditorium of building M,
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TAPANI SALONEN

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Renal Replacement Therapies

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Elämme kovia aikoja, ystävä hyvä.

—*Aku Anka* 4/1955

To the non-monetary determinants in life

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following four original publications, which are referred to in the text by their Roman numerals I–IV.

- I Salonen T, Reina T, Oksa H, Sintonen H, Pasternack A (2003): Cost analysis of renal replacement therapies in Finland. *Am J Kidney Dis* 42(6): 1228-38.
- II Salonen T, Reina T, Oksa H, Rissanen P, Pasternack A (2007): Alternative strategies to evaluate the cost-effectiveness of peritoneal dialysis and hemodialysis. *Int Urol Nephrol* 39(1): 289-98.
- III Salonen T, Piirto J, Reina T, Saha H, Pasternack A (2007): Implications of levels of serum mineral metabolism markers, albumin and C-reactive protein for treatment costs of patients on maintenance dialysis. *Nephron Clin Pract* 106(1): 17-23.
- IV Salonen T, Saha H (2014): Structured outpatient peritoneal catheter insertion is safe and cost-saving. *Perit Dial Int* 34(6):612-7.

ABBREVIATIONS

APD	automated peritoneal dialysis
CAPD	continuous ambulatory peritoneal dialysis
Ca	calcium
CBA	cost-benefit analysis
CE	cost-effectiveness
CEA	cost-effectiveness analysis
CER	cost-effectiveness ratio
CHD	in-centre hemodialysis
CRP	C-reactive protein
CTX	kidney transplant from a cadaveric donor
CU	cost-utility
CUA	cost-utility analysis
CKD	chronic kidney disease
CKD-MBD	chronic kidney disease-mineral and bone disorder
DCOR	Dialysis Clinical Outcomes Revisited
DOPPS	Dialysis Outcomes and Practice Patterns Study
EBPG	European Best Practice Guidelines
eGFR	estimated glomerular filtration rate
ERA-EDTA	European Renal Association/European Dialysis and Transplant Association
ESRD	end-stage renal disease
FHN	Frequent Hemodialysis Network
GDP	gross domestic product
HD	hemodialysis
HDF	hemodiafiltration
HFHD	high-flux hemodialysis
HHD	home-hemodialysis
HRQOL	health-related quality of life
ICER	incremental cost-effectiveness ratio
KDIGO	Kidney Disease: Improving Global Outcomes

K/DOQI	Kidney Disease Outcomes Quality Initiative
LTX	kidney transplant from a living donor
MDRD	Modification of Diet in Renal Disease
MICS	malnutrition-inflammation complex syndrome
MIS	Malnutrition-Inflammation Score
NHD	nocturnal hemodialysis
NHP	Nottingham Health Profile
NICE	National Institute for Health and Clinical Excellence
NRS 2002	Nutritional risk screening
P	phosphorus
PD	peritoneal dialysis
PDCI	peritoneal dialysis catheter insertion
PEW	protein-energy wasting
pmp	per million population
PTH	parathyroid hormone
QALY	quality-adjusted life-year
RRT	renal replacement therapy
SatHD	satellite hemodialysis
SC-HD	self-care hemodialysis
SDHD	short daily hemodialysis
SD	standard deviation
SEM	standard error of the mean
SF-36	Short Form Health Survey
SGA	Subjective Global Assessment of nutritional status
SIP	Sickness Impact Profile
TaUH	Tampere University Hospital
TTO	Time-Trade Off
TX	kidney transplantation
USRDS	United States Renal Data System
WHO	World Health Organization

ABSTRACT

Kidney failure is a severe condition which extensively affects patients' life by markedly increasing mortality and morbidity, causing symptoms which may impair health-related quality of life (HRQOL). Patients with end-stage kidney failure (also termed as stage 5 chronic kidney disease; CKD Stage 5) require renal replacement therapy (RRT) to maintain life. Options for RRT are hemodialysis (HD), peritoneal dialysis (PD) and kidney transplantation (TX). In dialysis therapies, despite improved prognosis compared with no treatment option, mortality among dialysis patients is greatly increased compared to the general population. On TX, improved survival and a better HRQOL are generally provided than on dialysis therapies and TX is considered the treatment of choice in suitable patients. However, all patients are not eligible for TX and demand for transplants chronically exceeds the available supply.

Considerable economic investments are required to provide RRT. In both HD and PD, material expenses and professional costs are high. In TX, the transplantation procedure requires considerable resources and after that, effective and expensive immunosuppressive medication is necessitated. In terms of mortality, morbidity and economics, kidney failure is one of the most severe chronic medical conditions and compared with general population, treating patients with CKD Stage 5 induces approximately a 20-fold cost increase.

Costs for medical care are rapidly increasing. Health economic evaluation, by providing methods to compare both outcomes and costs of alternative options, supports decision-makers to allocate limited resources as effectively as possible to maximize advantages. Cost-effectiveness analysis (CEA) is the most popular form of health economic research. In a CEA, outcomes of particular decision options are compared in terms of their cost per unit of health outcome achieved. Results are expressed as cost-effectiveness ratios (CER), e.g. cost per case prevented or cost per life-year gained. When comparing two strategies, utilizing incremental CER (ICER) is recommended. ICER describes additional costs required to achieve an extra unit outcome in one strategy compared to another. Cost-utility analysis (CUA) is a specific form of CEA, in which the quality of gained results is evaluated. In a CUA, outcome is commonly expressed as quality-adjusted life-years

(QALYs). QALYs are calculated by multiplying the amount of gained life-years with the quality (utility; ranging from 0 to 1) of those years.

The aims of this study were to determine costs and distribution of costs in various RRTs, to compare cost-effectiveness of HD with PD, to find associations between dialysis patients' treatment costs and serum levels of mineral metabolism markers, albumin and C-reactive protein and, finally, to compare outcomes and costs between inpatient and outpatient peritoneal dialysis catheter implantation.

Studies I and II comprised all adult ESRD patients who started their dialysis therapy 1991–1996 at Tampere University Hospital (TaUH). All use of health care resources was recorded. Of a total of 214 patients, 138 started with HD and 76 patients with PD. 55 patients received a kidney transplant during the study period. Costs (US\$) for the first six months in HD, PD and TX groups were 32566, 25504 and 38265 and for next six months 26272, 24218 and 7420, respectively. Costs for the second and third years were for HD 54140 and 54490, for PD 45262 and 49299, and in the TX group 11446 and 9240. In CEA, alternative strategies were applied to determine the end-points of observation. PD dominated over HD in three strategies (intention-to-treat, time on dialysis and time on primary modality). When the dialysis modality failure was considered death, ICER in HD was 444 041.

Patients in Study III were a subgroup of patients in Studies I and II. Subjects who had remained in for at least one year and with available laboratory results were included. 109 patients were identified. Laboratory results were obtained from the hospital's database. After controlling for patients' characteristics, there was no correlation between mineral metabolism markers and costs, but a trend towards lower cost (\pm SD) among patients who achieved the recommended targets of calcium (Ca), phosphorus (P) and parathyroid hormone (PTH) (US\$145 \pm 31) compared to those with non-optimal levels (US\$165 \pm 48, $p=0.095$) was found. In patients with at least one in-target PTH, costs were lower than in patients with constantly low PTH (US\$148 \pm 31 vs. 170 \pm 48; $p=0.01$). A positive correlation between CRP and costs and a negative correlation between Alb and costs was found.

In Study IV, costs and outcomes (within 90 days) were compared between inpatient and outpatient peritoneal dialysis catheter insertion (PDCI). All adult patients who were inserted a peritoneal dialysis catheter at TaUH 2004–2009 were included in the study. Altogether 106 PDCIs were performed during the follow-up, 46 were electively admitted patients (inpatient group) and 41 were placed on an outpatient basis (outpatient group). In 19 cases PDCI took place for other medical

reasons. 23 (22%) complications occurred within 30 days. Within 90 days, the cumulative rates of technique failure and infectious complication were 10% and 25% respectively. Differences in incidences of complications were statistically insignificant between inpatient and outpatient groups. Compared with the inpatient group, costs (\pm SEM) (EUR) of the PDCI process were significantly lower in the outpatient group (1346 ± 33 vs. 2320 ± 142 , $p < 0.000$).

In conclusion, treatment costs on PD may be slightly lower than costs on HD and compared with HD, PD may be a cost-effective treatment in eligible patients. The high initial costs for TX are balanced during the next months, after which costs for TX are markedly lower than for dialysis. Achieving recommended PTH levels may be associated with lower costs in dialysis patients and an outpatient PDCI is safe causing less cost than an inpatient PDCI.

TIIVISTELMÄ

Vaikea munuaisten vajaatoiminta aiheuttaa paljon elämänlaatua heikentäviä oireita ja potilaiden kuolleisuus ja sairastavuus on moninkertainen muuhun väestöön verrattuna. Vajaatoiminnan edetessä käy munuaistoiminta lopulta riittämättömäksi ja elämän ylläpitämiseksi tarvitaan munuaiskorvaushoitoa. Munuaistoimintaa korvaavia hoitomuotoja ovat hemodialyysi (HD), vatsakalvo- eli peritoneaalidialyysi (PD) sekä munuaisensiirto (TX). Dialyysihoidon avulla estetään potilaiden välitön menehtyminen munuaisten vajaatoimintaan, mutta kuolleisuus ja sairastavuus ovat edelleenkin paljon muuta väestöä korkeammat. Munuaisensiirron jälkeen potilaiden ennuste on parempi kuin dialyysihoidossa, mutta leikkaustoimenpide on raskas ja sen jälkeen tarvittava siirteen hylkimistä estävä lääkitys heikentää samalla elimistön puolustuskykyä. Kaikki potilaat eivät siten sovellu munuaisensiirtoon eikä siirteitä myöskään ole riittävästi saatavilla.

Dialyysi- ja munuaisensiirtopotilaiden hoito ja seuranta tapahtuu pääosin erikoissairaanhoidossa. Materiaali- ja laitekustannusten, ammattitaitoisen työvoiman tarpeen sekä runsaiden liitännäissairauksien vuoksi dialyysipotilaiden hoito on kallista. Munuaisensiirrostaikin aiheutuu merkittäviä kustannuksia; siirtoleikkaus on vaativa toimenpide ja sen jälkeen vaaditaan tiivistä ja säännöllistä seurantaa. Myös hylkimisenestolääkitystä on käytettävä jatkuvasti. Munuaiskorvaushoidossa olevien potilaiden terveydenhuoltokustannukset ovatkin keskimäärin n. 20-kertaiset muuhun väestöön verrattuna.

Terveystaloustieteellinen tutkimus arvioi erilaisten vaihtoehtojen, valintojen ja panostusten vaikutuksia terveydenhuollon tuloksiin ja kustannuksiin. Terveydenhuollon kustannukset kasvavat jatkuvasti, ja tutkimustieto auttaa päätöksentekijöitä kohdentamaan niukkenevat taloudelliset voimavarat mahdollisimman tehokkaasti. Yleisin terveystaloustieteellisen tutkimuksen muoto on kustannusvaikuttavuusanalyysi (CEA), jossa hoitoja arvioidaan kustannusvaikuttavuussuhteen (CER) avulla. CER kuvaa tarvittavien kustannusten määrän tiettyä lopputulosta kohden (esimerkiksi montako euroa maksaa saavutettu elinvuosi tai estetty tautitapaus). Kahta eri hoitoa verrattaessa on suositeltua määrittää inkrementaalinen kustannusvaikuttavuussuhde (ICER), joka tarkoittaa hoidossa koituvien lisäkustannusten ja saavutetun lisähyödyn suhdetta toiseen

hoitoon verrattuna. Kustannus-utiliteettianalysissä (CUA) arvioidaan laatuun suhteutettujen elinvuosien (QALY) kustannuksia. QALY lasketaan kertomalla saavutettujen elinvuosien määrä elämänlaatua kuvaavalla kertoimella, joka on arvoltaan välillä 0–1.

Tämän väitöskirjatyön tavoite oli määrittää munuaiskorvaushoidossa olevien potilaiden hoidon kustannukset ja kustannusten rakenne Tampereen yliopistollisessa sairaalassa, verrata kustannusvaikuttavuutta dialyysihoidomuotojen välillä, selvittää onko hoidon kustannusten ja kalsiumaineenvaihdunnan mittareiden, C-reaktiivisen proteiinin (CRP) tai albumiinin seerumipitoisuuksilla yhteyttä sekä selvittää tulokset ja kustannukset polikliinisessä ja osastolta käsin tapahtuvassa peritoneaalidialyysikatetrin laitossa (PDCI).

Osatöiden I ja II potilaina ovat kaikki täysi-ikäiset kroonikkodialyysihoidoon Tampereen yliopistollisessa sairaalassa vv. 1991–1996 otetut ureemikot, joita oli yhteensä 214. Heistä 138 aloitti HD:ssä ja 76 PD:ssä ja 55 potilasta sai munuaissirteen myöhemmin seurannan kuluessa. Terveyspalvelujen käyttö seuranta-aikana selvitettiin ja hinnoiteltiin palvelujen tuotantokustannusten mukaan. Kustannukset (US\$) ensimmäisen puolivuotisjakson aikana ryhmissä HD, PD and TX olivat 32566, 25504 ja 38265 ja seuraavan kuuden kuukauden aikana 26272, 24218 ja 7420. Toisen ja kolmannen vuoden kustannukset olivat HD:ssä 54140 ja 54490, PD:ssä 45262 ja 49299 ja TX:ssä 11446 ja 9240. Kustannusvaikuttavuusanalysissä verrattiin keskenään HD- ja PD-hoitoa. Seurannan päättymiskriteerit määriteltiin neljällä eri tavalla. Näistä kolmessa (hoitomuotojen vaihtoa ei huomioida, seuranta loppuu munuaissirtoon ja aika alkuperäisessä hoitomuodossa) PD dominoi: kustannuksia aiheutui vähemmän ja potilaiden elossapysymisen nuste oli parempi kuin HD:ssä. Kun hoidon epäonnistuminen rinnastettiin kuolemaan, oli HD-potilaiden elossapysyminen parempi kuin PD-potilailla, mutta HD:llä saavutettavan laskennallisen lisäelinvuoden hinnaksi (inkrementaalinen kustannusvaikuttavuussuhde; ICER) tuli 444 041.

Osatyön III potilasjoukko muodostettiin osatöiden I ja II aineistosta. Mukaan otettiin potilaat, joiden dialyysihoido oli kestänyt vähintään yhden vuoden ajan ja joiden laboratoriotulokset olivat käytettävissä; lukumääräksi muodostui 109. Kun ikä, taustasairaudet ja dialyysihoidomuoto vakioitiin, ei hoitokustannusten ja kalkkiaineenvaihduntaa kuvaavien mittaustulosten välillä ollut riippuvuussuhdetta. Potilailla, joiden tulokset olivat tavoitealueella, päivittäiset kustannukset (\pm SD) olivat hienokseltaan matalammat kuin niillä, joiden tulokset eivät olleet tavoitteessa, vaikkakaan ero ei ollut tilastollisesti merkitsevä (US\$ 145 ± 31 ja 165 ± 48 , $p=0.095$). Potilailla, joilla ainakin yksi parathormonipitoisuus oli tavoitealueella,

kustannukset olivat matalammat kuin niillä, joiden määritystulokset olivat jatkuvasti alle tavoitteen (US\$ 148 ± 31 ja 170 ± 48; p=0.01). CRP-pitoisuus ja kustannukset korreloivat keskenään ja albumiinipitoisuuden ja kustannusten välillä todettiin käänteinen korrelaatio.

Osatyössä IV verrattiin toisiinsa polikliinisen ja osastohoitojakson aikana tehtävän PDCI:n tuloksia ja kustannuksia. Vuosien 2004–2009 kuluessa yhteensä 106 aikuispotilaalle asetettiin PD-katetri. Heistä 46:lla toimenpide tehtiin ennaltasovitun osastojakson aikana ja 41 potilasta hoidettiin polikliinisesti. 19 potilasta oli osastohoidossa muun syyn vuoksi. 23 potilaalla todettiin katetriin liittyvä komplikaatio 30 vrk:n kuluessa toimenpiteestä. 90 vrk:n kuluessa PD-hoito epäonnistui 10 %:lla ja infektiokomplikaatio kehittyi 25 %:lle. Komplikaatioiden ilmaantumisessa ei ollut eroa osasto- ja polikliinisten potilaiden välillä. Kustannukset (euroa ± SEM) polikliinisilla potilailla olivat merkitsevästi matalammat kuin osastopotilailla (1346 ± 33 ja 2320 ± 142, p <0.000).

Väitöskirjan osatöiden yhteenvetona voidaan todeta hoitokustannusten olevan hieman matalampia PD-hoitoon valituilla potilailla kuin HD-potilailla, ja PD on kustannusvaikuttavaa hoitoa HD:iin verrattuna – niillä potilailla jotka tähän hoitoon soveltuvat. Munuaisensiirrosta kustannuksia kertyy alkuvaiheessa paljon, mutta ne vähenevät seuraavien kuukausien aikana, ja dialyysihoitoihin verrattuna saavutetaan kustannussäästöjä. Tavoitteessa oleva parathormonipitoisuus dialyysipotilailla saattaa liittyä pienempiin hoidon kustannuksiin. Polikliininen PD-katetrin laitto on yhtä turvallista mutta halvempaa kuin osastohoitojakson aikana tapahtuva toimenpide.

1 INTRODUCTION

Chronic kidney disease (CKD) is an irreversible and usually a progressive impairment in renal function. In mild kidney insufficiency patients most are asymptomatic but along with disease progression, several symptoms appear. In severe CKD, renal function is insufficient, removal of waste products is disordered and patients start to suffer from uremic symptoms which markedly affect health-related quality of life (HRQOL). Of heterogeneous uremic symptoms, fatigue, nausea, anorexia, itching, hypervolemia and neurologic disorders are the most prominent (National Kidney Foundation 2002; Levey et al. 2003; Levey et al. 2005). Various complications and consequences such as anemia, metabolic acidosis, hyperkalemia, disordered mineral metabolism and markedly increased risks of cardiovascular diseases are related with kidney failure and without treatment, the condition leads to death (Johnson and Feehally 2003). Unfortunately, there is no cure for CKD and patients with end-stage CKD (CKD Stage 5) need a renal replacement therapy (RRT) to maintain life (National Kidney Foundation 2002; Eriksen et al. 2006).

Options for RRT include dialysis therapy and kidney transplantation. In dialysis, two alternative modalities are available. In hemodialysis (HD) blood is pumped through an extracorporeal circuit which consists of blood lines and a dialyzer. In the dialyzer, blood dialysis fluid flow along opposite sides of a semi-permeable membrane. Diffusion gradient and hydrostatic pressure between the compartments result in a removal of waste products and fluid from the patient, and a partial but not complete improvement in disordered homeostasis (Cambi and David 1994). In peritoneal dialysis (PD), dialysis fluid is infused into the peritoneum cavity. Waste products and extra fluid transfer across the peritoneal membrane from the body to the dialysis solution. By draining the dialysate out and infusing fresh fluid, a sufficient gradient is maintained and as a net effect, water and solutes accumulated due to kidney failure are removed from the body (Pastan and Bailey 1998). In kidney transplantation (TX), patient suffering from CKD receives a kidney either from a living donor or from a brain-death donor. After donor nephrectomy, the transplant is usually placed in the recipient's iliac fossa and circulation and urine

flow are provided by vascular and ureteral anastomosis. To prevent rejection, immunosuppressive medication is required (Sharif et al. 2011).

In those patients who are selected to enter dialysis therapies, both HD and PD are reasonably effective in keeping patients alive when compared with no treatment option. Nevertheless, mortality in dialysis patients is much higher and HRQOL is impaired when compared with the general population. In TX patients, survival and HRQOL are better compared with patients treated with HD and PD, but they still are below figures found in general population. Not all patients are suitable for dialysis therapy or kidney transplantation. In patients with severe comorbidities and with an expected survival time of only a few months, a survival advantage or an improvement in quality of life is not gained by dialysis (Murtagh et al. 2007; Da Silva-Gane et al. 2012). Likewise, due to an increased risk of mortality during the first months after the transplantation procedure, TX is not a treatment of choice in the most elderly and comorbid patients (Wolfe et al. 1999).

To perform RRTs, considerable economic investments are required. Both in HD and PD, the need for treatment is continuous and both material expenses (such as devices, equipment, fluids and supplies) and professional costs are high. In TX patients, the transplantation procedure requires resources and causes costs. After that, there is a need for effective and expensive immunosuppressive medication. When measured by mortality, morbidity and economic aspects, kidney failure is one of the most severe chronic medical conditions and compared with non-dialysis patients, at least a 20-fold increase in costs are induced by end-stage CKD (Thamer et al. 1996; Nicholson and Roderick 2007; Sharif and Baboolal 2012).

The primary objective of a health care system is to deliver health care services. In some cases, savings may be induced (for instance, global eradication of poliomyelitis) (Bart et al. 1996) but in most cases, costs are caused by maintaining a functioning health care system and providing care. Globally, costs for medical care are increasing more rapidly than the growth of Gross Domestic Product, and even in the wealthiest countries, society's economic capacity to offer the best available treatment to all individuals will soon be exceeded (Erickson et al. 2010). The question is how much money a society is willing to invest in health care and how the limited resources can be targeted to gain the greatest benefits for the population.

Health economic evaluation provides methods to compare both outcomes and costs of alternative strategies. In a thorough health economic evaluation, all costs and outcomes are assessed and a sufficient time horizon is applied (Drummond et

al. 1987). In a complex setting, as state of health, measuring costs and consequences is not straightforward. A certain treatment may improve prognosis of the particular disease but, on the other hand, it may cause health-related adverse effects which should be taken into account as the outcomes are evaluated. Costs are different whether they are counted from the society's, provider's, payer's or patient's perspective. The question of time horizon is also important: Certain interventions or decisions today give rise to health effects and costs which may not occur immediately but they emerge several years afterwards and their impact may be insufficiently considered if only a limited period is evaluated.

The role of dialysis therapy is crucial in determining the societies' limits for medical treatment. In the United States end-stage CKD has remained the only diagnosis where treatment is universally reimbursed and granted on the basis of a diagnosis. Consequently, both in the United States and globally, the cost of dialysis therapy is broadly quoted as a benchmark for the willingness to pay threshold of medical technologies – the society should be obligated to reimburse for other treatments with at least similar costs and outcomes (Winkelmayer et al. 2002; Lee et al. 2009). This thesis and the literature reviewed in it focus firstly, on describing and evaluating health economic methods and, secondly, assessing costs related with various RRTs and conditions in dialysis patients. Costs for HD, PD and TX and distribution of costs in different modalities are presented. Survival, HRQOL and cost-effectiveness in various treatment modalities are described. Impact of levels of serum mineral metabolism markers, C-reactive protein and albumin on outcomes and costs in dialysis patients is discussed and, finally, different methods to insert a peritoneal dialysis catheter are evaluated.

2 REVIEW OF THE LITERATURE

2.1 Economic evaluation in health care

The interpretation of term "cost" can vary depending on the boundaries and perspective from which it is being measured (Haycox and Jones 1996). Oxford Dictionary of English defines cost as an amount that has to be paid or spent to buy or obtain something (Stevenson 2010). The economist's definition of cost in medical care relates to the value of resources consumed during the process of service provision in therapeutic area (Haycox and Jones 1996).

In health care, providing medical services induces costs. At unit-level, costs are produced by salaries, supplies, laboratory tests and medication. Institutional level refers to evaluation of both unit-level and overhead costs (infrastructure, maintenance and amortization). At health care system level, all use of resources is taken into account. This includes both institutional costs and costs for transportation, home care services etc. At society level, attempts are made to calculate additional costs caused by loss of productivity, inability to work, early retirement and premature death (Prichard 1997). Generally, costs are defined as direct and indirect costs. Direct costs include expenses for health care and they can further be divided into medical (treatment related) and non-medical (e.g. transport) cost. Indirect costs are not directly associated with health care but they stand for costs caused by loss of productivity, lowered incomes and disability payments. Intangible costs, which seldom are measured, refer to costs associated with items for which valuation is difficult such as pain or infertility (Schmid 1995).

The objective of a health care system is to provide an optimal mix of quality, access and cost (De Vecchi et al. 1999). On the other hand, costs for medical care are rapidly increasing and, on the other hand, resources are limited. Even in wealthy countries, all treatments cannot indefinitely be afforded to all individuals (Erickson et al. 2010). The question is, how the restricted resources can best be used to maximise the health benefits for the population. In response to scarcity, economic evaluation of medical care has increasingly been applied. Economic evaluation is a process of comparing courses of action in terms of both outcomes and costs (Drummond et al. 1987). By providing methods to compare costs and

benefits of alternative strategies, economic evaluation functions as an instrument offering essential information for decision-makers.

2.1.1 Cost analysis

Cost analysis is the description of the costs of a program or treatment. In a cost analysis, expenses are identified to see how much is spent on a particular treatment or program but the outcome is not involved. As a descriptive non-comparing analysis, cost analysis is not regarded as a true economic evaluation (Drummond et al. 1987).

2.1.2 Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) contains both cost calculations and measurements of the effects gained. In a CEA the outcomes of particular decision options are compared in terms of their cost (C_1 , C_2) per unit of health outcome (E_1 , E_2) achieved. Results are expressed as cost-effectiveness ratios (CER), e.g. cost per case prevented or cost per life-year gained.

$$CER_1 = \frac{C_1}{E_1}$$

$$CER_2 = \frac{C_2}{E_2}$$

When comparing two strategies, by dividing differences in costs (C_1 , C_2) by differences in outcomes (E_1 , E_2), incremental CER (ICER) is given. As the ratio of change of costs to change of results, incremental CER describes additional costs required to achieve an extra unit outcome in one strategy compared to another. Depending on differences in costs and outcomes, the ICER can be both positive and negative:

$$ICER = \frac{C_2 - C_1}{E_2 - E_1}$$

CEA is the most reasonable analysis design when the goal is to identify the most cost-effective strategy from among a set of options that produce a common outcome. (Drummond et al. 1987)

2.1.3 Cost-utility analysis

A specific form of CEA is a cost-utility analysis (CUA), in which not only the amount but also the quality of gained results is evaluated. In a CUA, outcome is measured in healthy year equivalents; commonly expressed as quality-adjusted life-years (QALYs). QALYs are calculated by multiplying data on the life years gained with a numerical value (utility) reflecting the quality of those years. As a function of length of life and health related quality of life (HRQOL), QALY is an attempt to combine the value of these attributes to a single index number (Rosner 2013). In general, utilities can range from 0 (equivalent to death) to 1 (equivalent to perfect health). Values are usually obtained from samples of patients or the population in general (Drummond et al. 1987). Two years of life in a health state judged to be halfway between death and full health would be equivalent to one year in full health. As quality of life is taken into account, CUA is claimed to be the most effective study design when comparing strategies which produce different health outcomes (Schmid 1995).

2.1.4 Methods to assess quality of life

Although HRQOL cannot be measured directly, several questionnaires have been developed from which utilities can be derived (Hawthorne et al. 1999; Peeters et al. 2000; Sintonen 2001; Brazier et al. 2002; Feeny et al. 2002). However, most of these measures have been designed for use in clinical research, not for economic evaluation. Of standardised questionnaires, Short Form Health Survey (SF-36) is one of the most widely used instruments. In SF-36 patient's health is assessed across several dimensions to provide an aggregate summary (Brazier et al. 2002). The Sickness Impact Profile (SIP), the Campbell Index of Well-Being and the Nottingham Health Profile (NHP) are examples of other questionnaires. The SIP contains 136 "yes and "no" questions and in the Campbell Index of Well-Being there are 10 questions that are ranked on a 7-point scale (Hornberger et al. 1992). The NHP comprises 38 statements assessing perceived emotional, physical and social problems and their impact on daily activities (Hunt et al. 1985). The 15D is a

self-administered 15-dimensional and standardized instrument that has been found to perform equally well as the NHP (Sintonen 2001). For patients with kidney disease, there are specifically developed questionnaires providing scores for general mental and physical health and including also kidney-disease specific domains (Laupacis et al. 1992; Hays et al. 1994).

The Standard Gamble and the Time Trade-Off (TTO) techniques are not based on profiles produced by questionnaires but patients are faced with a single question. In the Standard Gamble, patients are requested to consider a new hypothetical device that could completely cure the particular medical problem (renal disease, for instance). Then, they are asked to figure what chance of immediate painless death they would be willing to accept before refusing to use the device. In the Time Trade-Off, the imaginary device provides, again, a complete cure but, instead of creating the risk of immediate death, it shortens life. Subjects are asked how many years they are willing to forego before refusing to use the device. In other words, patients provide their estimates of the highest acceptable risk and these estimates are further utilized to generate HRQOL. (Hornberger et al. 1992)

2.1.5 Cost-benefit analysis

In cost-benefit analysis (CBA) both costs and outcomes are measured in monetary units. All of the costs are added up and subtracted from the total value of outcomes. Value of benefits minus costs and the ratio between the two are called net present value and cost-benefit ratio, respectively. The decision rule of CBA is clear: undertake an intervention if the value of its benefits exceeds its costs. The problem in performing cost-benefit analyses in health care is valuing the outcomes, such as improving health and extending life, in monetary terms (Higgins and Harris 2012). CBA can be used to evaluate a single option (assessing whether benefits exceed costs) whereas CEA and CUA always compare two or more options. Since all costs and benefits should be included and valued in a CBA, this analysis becomes complex and difficult to perform.

2.1.6 Comparative effectiveness research

Concept of comparative effectiveness research was introduced recently. It is defined as the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition, or to improve the delivery of care. The purpose of comparative effectiveness research is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels (Sox and Greenfield 2009). By definition, outcomes (benefits and harms) but not costs are evaluated in comparative effectiveness research and it cannot be regarded as economic evaluation.

2.1.7 Discounting

Generally, current costs and events are regarded more important receiving more weight than future costs and consequences, a phenomenon termed as a positive rate of time preference. Discounting is a concept based on time preference and it refers to the fact that money is preferred to possess now rather than later. In health care, costs and subsequent outcomes may be spread out over multiple years. For example, current costs for vaccination need to be compared with benefits of prevented cases and with reduced healthcare costs in the future. In discounting process the value of a future outcome is adjusted to its present value (Simoens 2009).

To illustrate the effect of discounting, we may consider a programme which costs EUR 1000 in three consecutive years (Table 1). When discounting the total sum of 3000 by frequently applied 5%, this equals a present value of EUR 2852,50:

Table 1. Effect of discounting

	Actual costs (EUR)	Discounting process (discount rate 5%/year)	Discounted costs (EUR)
Present time	1000	–	1000
Present time + 1 year	1000	$(1-0,05)^1 \times 1000$	950
Present time + 2 years	1000	$(1-0,05)^2 \times 1000$	902,50
Sum	3000		2852,50

Discounting may be restricted in monetary terms only, but discounting of health outcomes has been recommended as well (Brouwer et al. 2005). The rate at which costs and outcomes are discounted may substantially affect CER. Attaching lower weight (i.e. using higher discount rate) in future health makes preventive medicine, which comprises years long time horizon between interventions and benefits, seem less cost effective and incorporates a risk of undervaluing future health in decision making (Brouwer et al. 2005). For instance, CERs of meningococcal vaccination campaign in England and Wales varied markedly depending on discount rates applied. Discount rates 1,5% for health and 6% for costs produced CER (UK Pounds/life year gained) 3845 and discounting both costs and health equally at 6% resulted in CER 15 710, respectively (Trotter and Edmunds 2002).

Guidelines recommend that costs and effects should be discounted equally in studies having time horizons longer than one year, irrespective whether the effects are expressed in money terms or life years gained. Reporting of the used discount rate as well as performing sensitivity analyses by using different discount rates is also recommended (Drummond et al. 1996; Brouwer et al. 2005). Usually, annual discount rate 3–6% is applied and a common rate in the literature is 5% in year (Drummond et al. 1996). However, e.g. HRQOL is assumed to be linear and rationality of processing a linear parameter by an exponential discount rate has been questioned (Ganiats et al. 2000; Attema et al. 2012).

Most analyst have recommended that benefits and costs should discounted similarly, but several economists have argued that this is not appropriate. The main point in questioning is that since health does not have monetary measureable value, it neither is a resource that can be traded or invested to produce more health in the future. On the other hand, health damaging activities like smoking and heavy drinking suggest that people actually attach less weight in their future health and they are, indeed, discounting their future health. Also, when applying lower discount rates for effects than for costs, postponing any given option would become attractive: costs will decrease as they were shifted further whereas future benefit would be valued the same as today, no matter when they occurred. An infinite postponement will be theoretically the most optimal choice. This practically undesirable effect is termed as postponing paradox (Brouwer et al. 2005).

2.1.8 Markov modelling

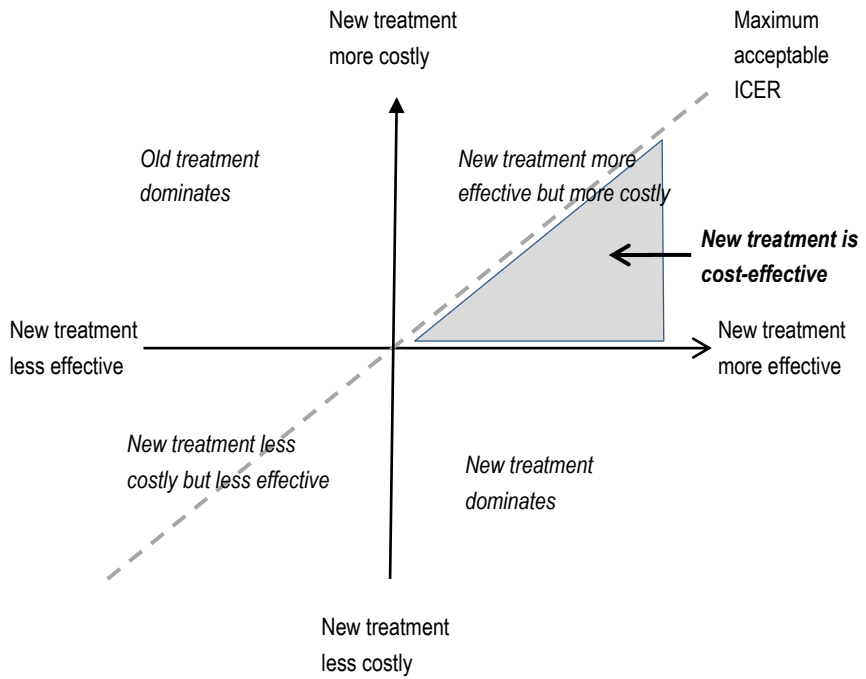
An economic evaluation can be carried out alongside a clinical trial. Ideally, a trial reaches adequate power to detect treatment-related differences in costs and outcomes and a sufficient time horizon is obtained. In practice, essential parameters may be inadequately estimated in clinical trials to make economic decisions. Both the synthesis of data deriving from various sources and extrapolation of data is often required. Modelling is a frequently applied tool to evaluate costs and outcomes over time. A particular type of model widely utilized is the Markov model. Markov models are generally used to simulate the progression of chronic disease. The particular disease is divided into various states and transition probabilities between these states over a certain time period known as a Markov cycle. In case of renal replacement therapies, for example, the alternative states are dialysis, renal transplantation and death. Costs associated with different states, transitions, procedures and other treatment related situations are determined. By running the model with a cohort including a large number of hypothetical patients and repeating multiple cycles, costs and outcomes over a certain period can be estimated and also the impact of various decisions and interventions can be assessed (Briggs and Sculpher 1998). Economic modelling is a relatively cheap and effective way to synthesize existing data, but results naturally depend on the reliability of variables incorporated into the model and on the accuracy by which the model is able to represent the course of particular disease. Inaccurate input provides inaccurate outcomes.

2.1.9 Willingness to pay

Cost-effectiveness (or cost-utility) can be illustrated graphically (Figure 1) (Black 1990). The difference in effectiveness (or utility) between two options is portrayed on the horizontal axis and the cost difference between the two is on the vertical axis, respectively. The point representing the differences in effectiveness and costs falls into one of the four quadrants. An option, which is more effective and less costly than the comparator, is termed as dominating. In cases which are both more effective and more costly than alternative options, society's cost-effectiveness-threshold determines whether the option will be adopted or not. Such a threshold represents the maximum amount which the authorities are willing to pay for a

treatment (maximum acceptable ICER). Options falling below this threshold are termed cost-effective.

Figure 1. Graphical illustration of cost-effectiveness



In some countries, authorities have specified certain cost-effectiveness thresholds and in some cases they can be determined from reimbursement decisions. In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) have applied a threshold value of (Pounds) 20 000/QALY and health technologies exceeding 30 000/QALY have been unlikely to be recommended (Raftery 2006). In the United States a figure of (US\$) 50 000/QALY has commonly been used (Grosse 2008) and the magnitude was set on the basis of the estimated annual cost of caring for a dialysis patient (Winkelmayer et al. 2002). This number has been used as a benchmark over several years regardless of inflation and its arbitrariness and inaccuracy has been noted (Hirth et al. 2000). Recently, it has been suggested that while the foundations of \$50 000 threshold are questionable, arguments for abandoning it exist. Instead of a fixed number, the threshold should vary across payers, populations and procedures (Bridges et al. 2010). World Health Organization (WHO) has recommended adopting threshold of 1 to 3 times of local gross domestic product (GDP) per capita (Tan-Torres Edejer et al. 2003).

2.1.10 Question of perspective

It is important to recognize the perspective from which an economic analysis was conducted. In some cases, outcomes may be straightforward to measure. In the complex setting of health care, relationships between inputs and outputs may markedly vary depending on the selected viewpoint. When taking a payer's perspective, costs are measured as reimbursements, which depend on accounting methods between different organizations, contracts with suppliers and profits achieved by facilities. From a provider's perspective, absolute production costs of a certain treatment or technology can be determined and they may substantially differ from its fixed amount of reimbursement. From a patient's perspective, costs for outpatient medication, other copayments and home care after discharge are important while they are irrelevant from the government's or hospital's viewpoint. Conclusions and decisions from a particular perspective are supported by information provided by the use of that certain perspective, but studies which have been conducted from different viewpoints are not comparable.

Applying a societal perspective has been suggested in order to consider all relevant costs and to avoid biases that may be incorporated in a narrower approach (Russell et al. 1996). Societal perspective considers all health effects and costs that are caused by a particular intervention; both benefits and harms are included. This

approach implies that not only direct treatment-related or program-related costs need to be processed but also expenses that are not included in the health-care sector or financed by the health care budget (such as productivity costs and costs for transport) are taken into account. Adopting a two-perspective approach has been suggested: presenting one CER following health care perspective and another CER following the common societal perspective. The health care perspective may be beneficial for the decision makers and the societal approach evaluates consequences of given decision in a broader perspective (Brouwer et al. 2006).

2.2 Renal replacement therapies

Chronic kidney disease (CKD) is a heterogeneous group of disorders characterized by alterations in kidney structure and function (National Kidney Foundation 2002; Levey et al. 2003; Levey et al. 2005). Usually CKD is a progressive condition and in some patients – but not deterministically in all – it leads to kidney failure, severely impaired kidney function, also known as CKD Stage 5 (National Kidney Foundation 2002; Eriksen et al. 2006). In a mild renal insufficiency patients usually are asymptomatic and as such, renal disease is not clinically apparent. The onset of end-stage CKD results in constellation of signs and symptoms referred to as uraemia. Manifestations of uraemic state include nausea, anorexia, volume overload and central nervous system disorders ranging from lethargy to death. Several complications are related with CKD including anaemia, hyperparathyroidism and markedly increased risks for cardiovascular diseases, infections, cognitive impairment and impaired physical condition (Johnson and Feehally 2003).

There is no cure for CKD and therapy is focused to slow the rate of progression of CKD with antihypertensive and antiproteinuric treatment. Patients with kidney failure require renal replacement therapy (RRT) to maintain life. Initiation of RRT – when medically indicated – should begin before kidney disease has advanced to the point where life-threatening complications occur. RRT aims both to prolong survival and to improve the HRQOL experienced by patients. Options for renal replacement therapies are hemodialysis, peritoneal dialysis and kidney transplantation.

2.2.1 Hemodialysis

During hemodialysis (HD), anticoagulated blood is pumped through an external filter (dialyzer). Diffusion of solutes between the blood and a dialysis solution results in the removal of metabolic waste products and the replenishment of body buffers. By means of adjustments in the transmembrane pressure across the dialyzer, removal of fluid from the plasma into the dialysis solution (ultrafiltration) can be controlled. HD was first introduced in 1960 for treatment of chronic uraemia and treatment sessions lasted for 12 to 18 hours every 10 to 15 days out of necessity (Scribner et al. 1960; Cambi and David 1994).

At present, hemodialysis can either be performed in hospital (in-centre hemodialysis, CHD; typically 3 weekly treatments of 4 to 5 hours) or by a patient at home (home hemodialysis, HHD). Home hemodialysis offers the opportunity to tailor the treatment regimen to individual requirements. In satellite hemodialysis (SatHD) care is organized and managed by nephrological clinics (university and central hospitals in Finland), but physically the treatment takes place in health centres or community hospitals. Sometimes patients are encouraged to participate in their own treatment at their hemodialysis units to maintain their performance and also to alleviate nurses' work. This is called self-care hemodialysis (SC-HD). Intensification of HD, when needed, is achieved by increasing frequency of therapy or duration of treatment or both and it is easily managed in HHD by applying short daily hemodialysis (SDHD) or nocturnal hemodialysis (NHD). To increase efficacy of conventional HD, novel techniques including hemodiafiltration (HDF) and high-flux hemodialysis (HFHD) have been developed.

To effectively remove waste products in chronic hemodialysis, a sufficient blood flow through the dialyzer must be provided. Therefore, there is the necessity for permanent vascular access, which is established by a catheter in a large vein or by arteriovenous fistula. Arteriovenous fistula can be constructed by using patient's artery and vein or by implanting a vascular graft made of prosthetic material.

2.2.2 Peritoneal dialysis

In peritoneal dialysis (PD), physiologic dialysis solution is infused through a catheter into the peritoneum cavity. Diffusive solute transport occurs across the peritoneal membrane and waste products transfer from the body into the dialysis solution. Diffusion gradient is maintained by draining the dialysate and replacing it with fresh fluid. Removal of fluid (ultrafiltration) from the body is provided by

osmolar gradient between body fluids and dialysate, typically achieved by glucose added to the dialysis solution (Pastan and Bailey 1998). In PD, a peritoneal catheter is required. Typically, a plastic catheter is implanted in the peritoneal cavity and anchored in the subcutaneous tissues. In implantation, open surgery, laparoscopic technique and radiological insertion may be applied (Wright et al. 1999; Negoj et al. 2006; Brunier et al. 2010).

Early clinical experience begins in 1923 when Ganter described improvement of condition in a uremic guinea pig after infusion and removal of saline in peritoneal cavity. First human patient was treated experimentally 1927 (Ganter 1923; Teschner et al. 2004). Chronic peritoneal dialysis was started in the 1960s and during the 1970s, after remarkable development in the access devices, PD became extensively clinically available (Popovich et al. 1978).

PD has two main treatment varieties: in continuous ambulatory peritoneal dialysis (CAPD) dialysis fluids are exchanged manually, usually four exchanges of 2 litres each of dialysate daily. However, dialysis may be inadequate especially in large patients. Automated peritoneal dialysis (APD), in which a cyclor infuses and drains dialysate at night, has gained popularity in recent years. In APD, fluid volume and number of cycles are tailored individually to optimize the efficacy of dialysis. It provides therapy without interruptions in daily routines (Daugirdas et al. 2007). Both CAPD and APD are mostly carried out by patients themselves at home. For those patients who are unable to perform the treatment and support is required, assisted PD provided by family members or visiting nurses is the therapy of choice.

Due to a straight connection from outside to the peritoneal cavity, peritonitis is a common and serious complication of PD. Exit-site infections, mechanical complications (hernia formation, fluid leak) and metabolic complications also occur. Dialysis and management of fluid overload may be insufficient in some patients (Daugirdas and Blake 2007). Modality switch from PD to HD is occasionally necessitated by complications.

2.2.3 Kidney transplantation

Immunologic aspects are closely related to organ transplantation. The principal function of the immune system is to defend against infections and fundamental to this capacity is to discriminate between self and nonself antigens. Transplanted tissue from a genetically different individual is immediately recognized in the body and an immune response mediated by lymphocytes is stimulated resulting in

rejection of the foreign material (2010). The first successful kidney transplantation was performed in 1954 between two identical twins (Merrill et al. 1956; Murray 2011) but due to the inability to medically control the human immune response the number of procedures remained low for years. From the 1960s, immunosuppression with azathioprine and corticosteroids enabled transplantations between immunologically non-identical individuals but still up to 40% of grafts were lost by the first year. The introduction of calcineurin inhibitor cyclosporine, a new potent immunosuppressant, in the early 1980s resulted in a remarkably improved prognosis leading to one year graft-survival rate of 80%. From the 1990s, emergence of the antiproliferative agent mycophenolate mofetil, more potent calcineurin inhibitor tacrolimus, the mammalian target of rapamycin inhibitors sirolimus and (post 2000) everolimus have been added to the standard immunosuppressive armamentarium along with monoclonal antibodies and other protein immunosuppressives. Effective medication, improved organ matching and preservation and chemoprophylaxis of opportunistic infections have all resulted in a progressive improvement in graft and patient survival (Sharif et al. 2011). Nowadays renal transplantation is considered as the standard treatment for ESRD in suitable patients.

Donor organs can be obtained from cadaveric sources or from living donors. Cadaveric transplants (CTX) are kidneys from brain-dead donors. Brain-death is defined as a condition, in which patient's cerebral functions are irreversibly lost but vital functions ventilation and circulation are artificially maintained by intensive care treatment. Many countries – including most European countries – have implemented transplantation laws which allow transplantation of organs from brain-dead donors (Haupt and Rudolf 1999). Usually both the kidneys are removed in a nephrectomy and they are further transplanted to two recipients. Living donor transplantation occurs when a person freely donates a kidney to someone in need of a transplant. Usually, transplantation takes place between family members such as spouses, siblings or from a parent to a child. Kidneys from living donors (LTX) are transplanted electively and they have certain advantages. With good planning, injury caused by ischemia can mostly be avoided. Compared with CTX, a delayed graft function is more uncommon and long term survival and HRQOL are superior in LTX (Lamb et al. 2011; Matas 2014).

Demand for kidney transplants chronically exceeds the available supply and worldwide both the number of patients on waiting list and the time on waiting list is increasing. To cover the shortage of organs, many centres have expanded the criteria for acceptable donors. Kidneys from older donors with certain

comorbidities with less than optimal function have progressively been utilized (Veroux et al. 2009) and also donation after cardiac death (donors with nonbeating hearts) has been successfully practiced (Morrissey et al. 2014).

2.3 Survival in renal replacement therapies

2.3.1 Survival in dialysis modalities

Despite improvements in dialysis technology, mortality among dialysis patients remains high. In an early report (data deriving from 1960s), Moorhead et al found overall 80,7% five-year survival in 109 patients admitted to RRT. Patients' characteristics were not reported (Moorhead et al. 1970). Thereinafter, older and sicker patients have been permitted to enter RRT (Himmelfarb and Ikizler 2010). Consequently, life expectancy in dialysis patients is markedly reduced: In 1993 it was estimated to be 7,1 years for patients at age 49 (reduced by 23 years compared to general population) and 4,3 years for patients at age 59 (reduced by 17 years), respectively (United States Renal Data System 1993). Between 1993 and 2003 there was little improvement in first-year death rates in ESRD patients, but between 2003 and 2009 these rates fell more than 14%. Still, mortality among ESRD patients remains ten times higher than in similar patients without kidney failure and three-year survival after the start of ESRD therapy is only 51%. Cardiovascular diseases and infections are the most important causes of death among dialysis patients (Collins et al. 2013).

When comparing survival between HD and PD, conflicting results have been yielded. A higher risk of death on PD, particularly in female diabetics has been found in some studies (Held et al. 1994; Bloembergen et al. 1995; Collins et al. 1999; Friedman 2003; Jaar et al. 2005; Vonesh et al. 2006) but contrary results have also been reported (Gentil et al. 1991; Fenton et al. 1997). These studies mostly derive from the 1990s and substantial reduction in mortality rates among PD patients has been demonstrated thereafter (Mehrotra et al. 2007; Jiwakanon et al. 2010). Similar survival rates on PD and on HD up to 60 months after adjusting patients' characteristics were recently presented in the United States Renal Data System (USRDS) 2012 Annual Report (Collins et al. 2013). Weinhandl et al reported equal adjusted 4-year survival (48% on HD and 47% on PD) in a study including over 6300 pairs of incident HD and PD patients (Weinhandl et al. 2010)

and a USRDS database study, which examined survival trends on HD and on PD did not find difference in the most recent patient cohorts (Mehrotra et al. 2011). In patients awaiting kidney transplantation, equal mortality on HD and on PD was found. However, among patients with body mass index >26 kg/m², selection of PD vs. HD was associated with a slightly increased risk of death (Inrig et al. 2006).

In a recent Finnish study, no significant difference in survival between dialysis modalities was found: Altogether 4463 adult patients entered RRT in Finland between 2000 and 2009 and dialysis modality was defined on an intention-to-treat basis. Patients' median survival time was 5,2 years. Without adjustment for confounding factors, relative risk of death of PD patients was lower compared with patients in HD, but this difference did not remain after comprehensive adjustment for 26 variables. The authors concluded that PD is associated with several factors generally related to good prognosis. (Haapio et al. 2013)

Especially the rate of cardiovascular morbidity and mortality are dramatically higher among ESRD patients than in the population generally. Even after adjustments for confounding factors, cardiovascular mortality increases 10-fold (Levin and Foley 2000). In registry data derived in the UK, the relative risk of death in RRT compared with the general population was 30,1 at age 25–29 and 4,6 at age 80–84 (Ansell et al. 2009). In 1974 Lindner et al (Lindner et al. 1974) found markedly accelerated progression of atherosclerosis on patients who had been in prolonged maintenance hemodialysis. Since then, vascular calcification has been found to be the major contributor to cardiovascular disease and a strong prognostic marker of mortality in patients with CKD (Lowrie and Lew 1990; Block et al. 1998; Ganesh et al. 2001; Marco et al. 2003; Guerin et al. 2008; Mizobuchi et al. 2009; Pai and Giachelli 2010). Evidence is accumulating that it is renal insufficiency in itself which stimulates vascular calcification and is the promoting risk factor for cardiovascular mortality (Shulman et al. 1989; Meier-Kriesche et al. 2003; Wannamethee et al. 2006; Ninomiya et al. 2009; Rinat et al. 2010; van der Velde et al. 2010; Delles and Jardine. 2011; Takeshita et al. 2012; Fang et al. 2013; Gauthier-Bastien et al. 2013; Svensson et al. 2013; Yahalom et al. 2013).

The CKD population is aged and prevalence of type II diabetes is high, but the classical risk factors alone do not adequately explain the high prevalence of cardiovascular diseases. An additional explanation to the markedly increased cardiovascular morbidity in CKD may be the impact of non-traditional risk factors, which are highly prevalent in CKD patients and which directly promote atherogenesis and endothelial dysfunction (Kalantar-Zadeh et al. 2006). Mineral metabolism disorders, protein wasting and inflammation are regarded as major

non-traditional risk factors (Stenvinkel 2002; Block et al. 2004; Kovesdy et al. 2009). In this context, the phenomenon termed as reverse epidemiology has been introduced (Kalantar-Zadeh et al. 2003). A high body mass index and an elevated concentration of serum cholesterol are associated with an increased cardiovascular risk in the general population, but paradoxically their effect is in the opposite direction in dialysis patients. The possible mechanism may be the relationship of protein wasting-malnutrition-inflammation complex with cardiovascular morbidity. Short-term risk of death is markedly increased in dialysis patients with chronic inflammation and protein wasting. High serum cholesterol level and obesity indicate absence of both protein deficiency and chronic inflammation and this profit outweighs the risks normally related to these conditions (Liu et al. 2004). However, improved survival associated with hypercholesterolemia was evident only during the first year of follow-up in a recent Dutch study including 1191 dialysis patients (Chmielewski et al. 2011).

Intensification of dialysis enhances clearance of solutes and it has been hypothesized that an increased dose of dialysis would turn to better clinical outcomes. However, in a large randomized trial including 1846 HD patients (the HEMO study), high dose of dialysis or the use of high-flux dialyzer did not have any effect on survival or hospitalization compared with patients receiving conventional thrice-weekly HD (Eknoyan et al. 2002). No improvements in HRQOL (Unruh et al. 2004) or nutritional status (Rocco et al. 2004) were found either. Contrary, in the Frequent Hemodialysis Network (FHN) Daily Trial 125 patients were assigned to undergo HD six times per week and 120 patients three times per week. After 12 months follow-up, frequent HD was associated with significantly lower risk of death (Chertow et al. 2010). FHN Daily Trial was a prospective randomized trial with a companion FHN Nocturnal Trial. In the FHN Nocturnal Study altogether 87 were randomized either to conventional thrice-weekly HD or nocturnal six times per week HD. Parameters measuring efficacy of HD were significantly better in the nocturnal group but – contrary to Daily Study with otherwise identical setting – no difference in death rates was found. However, follow-up lasted for only 12 months (Rocco et al. 2011). When assessing outcomes in SatHD compared with conventional CHD, a comprehensive evaluation conducted in the United Kingdom did not find any significant differences (Roderick et al. 2005). In a French study (Arkouche et al. 1999), results of twenty-five years of experience with out-centre HD were reported. Compared to CHD, better survival was found in out-centre HD (HHD and SC-HD), but the authors also speculated results being related in part to the bias of selection of patients.

In PD, a modified prescription to achieve a high peritoneal clearance did not improve survival over conventional CAPD in a large controlled prospective Mexican study (the ADEMEX Study) (Paniagua et al. 2002). APD, despite more frequent exchanges and better fluid management, has also been found ineffective in providing survival advantage over CAPD in observational or small randomized studies (Rabindranath et al. 2007; Michels et al. 2009; Cnossen et al. 2010).

2.3.2 Survival and kidney transplantation

In 1973 Lowrie et al (Lowrie et al. 1973) compared survival of kidney transplant recipients and dialysis patients. They found that two-year survival was significantly better in recipients of transplants from living related donors and in dialysis patients than in those who received a CTX. Since then, outcomes in cadaveric kidney transplantation have remarkably improved. Numerous studies have indicated that kidney transplantation – both CTX and LTX – provides a significant survival advantage over maintenance dialysis and the risk of cardiovascular events is also reduced (Disney 1995; Locatelli et al. 1995; Teraoka et al. 1995; McDonald and Russ 2002; Schon et al. 2004; Merion et al. 2005; Snyder et al. 2006; Chavers et al. 2007; Sorensen et al. 2007; Ansell et al. 2009; Kramer et al. 2009; Stel et al. 2009).

Outcomes of kidney transplantation as compared with dialysis were evaluated recently in a systematic review. This comprehensive analysis included 110 eligible studies from 1950 to 2010 to summarize the clinically relevant benefits of transplantation over dialysis treatment. 77 studies including 163 patient cohorts reported unadjusted comparisons of mortality between TX and dialysis. Of these, 76% found a significantly lower risk of death in TX whereas 7% found a lower risk with dialysis. In 23 studies with 38 patient cohorts, risk rates were derived from adjusted data and in 79% mortality was lower with TX, 21% reported non-significant differences. When regarding the year of publication, the relative benefit achieved by transplantation seemed to be markedly increasing over time. The authors concluded that despite heterogeneity caused possibly by a wide range of studies with various settings, dialysis modalities and populations, the magnitude and consistency of the benefits associated with transplantation is obvious, even if this benefit cannot be conveyed in a single summary measure. (Tonelli et al. 2011)

To assess the extent to which TX increases survival compared with dialysis treatment is not straightforward. Several factors influence on access to TX. Transplant recipients are derived from a highly selected subgroup of healthier,

younger and richer than those dialysis patients who are not selected (Kasiske et al. 1998). In a North American study, patients with cardiovascular diseases and obesity showed lower TX rates compared with patients without these conditions and also socioeconomic factors such as female sex, lower income and nonwhite race independently associated with lower probability of receiving a transplant (Gaylin et al. 1993). The selection bias obviously affects survival outcomes and causes distortion favouring TX. To avoid this, Wolfe et al conducted a study comparing survival of patients receiving a transplant with survival of those awaiting transplantation in 1999. The long-term mortality was 48 to 82 percent lower in transplant recipients compared to the patients on the list waiting for a transplant. Benefits were relatively larger among patients aged 20 to 39 and among young patients with diabetes. The increased short-term risk of death associated with surgery and high-dose immunosuppressive treatment remained elevated until 106 days after TX. The subsequent decrease in the risk of death counterbalanced the initially high rates and after day 244, TX resulted in a cumulative survival benefit. The survival advantage among recipients compared to patients on a waiting list was apparent regardless of age, sex, race or cause of ESRD. The authors' conclusion was that TX improved longevity in all groups of recipients (Wolfe et al. 1999). However, the actual survival advantage achieved by TX is not known. In observational studies, the bias caused by selection can not be completely avoided.

The results of Wolfe have been confirmed in several studies. Among 174 patients over age 60 who were accepted on a waiting list, the 5-year survival was 90% for the TX group and 27% for those who continued to undergo dialysis (Johnson et al. 2000). Snyder et al (Snyder et al. 2006) compared outcomes of 43427 adult TX recipients with 53309 adult dialysis patients who were placed on a waiting list. Mortality and incidence of peripheral arterial disease (PAD) were significantly higher in the dialysis group. Both PAD and dialysis therapy seemed to be independent risk factors for death. Risk was increased among diabetics and non-diabetics and duration of dialysis was associated with the risk of PAD. The authors concluded that early and even preemptive TX may help to reduce the risk of PAD. Glanton et al (Glanton et al. 2003) studied dialysis patients with body mass index >30 kg/m² enrolled on the waiting list. They found significantly lower mortality after TX compared with those remaining on the waiting list. On the other hand, when comparing TX and nocturnal HHD, which provides more physiological restorative potential than conventional HD does, Pauly et al demonstrated no difference in survival with HHD and CTX. The recipients of LTX had the lowest risk of death. The authors stated that the survival advantage of TX varies with

donor source and survival equivalent to CTX may be achievable by intensification of dialysis with HHD. (Pauly et al. 2009)

In a recent Finnish study, duration of pretransplant dialysis was associated with an increased risk of death in TX patients. Altogether 3105 patients who received their first kidney transplantation were included in this observational study. After adjustment for confounding factors, duration of dialysis remained an independent risk factor of death after TX, risk ratio was 1,23 per 1-year increase in dialysis duration. The length of pretransplant dialysis period was associated with mortality resulting from cardiovascular diseases. Correlation between dialysis duration and non-cardiovascular mortality was not found (Helanterä et al. 2014).

The number of elderly patients entering RRT is increasing. To assess the survival advantage of TX over dialysis in elderly patients, 325 dialysis patients aged over 60 years and accepted onto transplant waiting list were followed in Scotland. 39% received a transplant; waiting time was on average 250 days. Survival was better in patients who received a transplant (relative risk of death 0,35) compared with those who continued dialysis and life expectancies were 8,2 and 4,3 years in TX and dialysis patients. Patients who received a transplant were younger and they had less cardiovascular diseases compared with dialysis patients. Nevertheless, the authors concluded that the analysis suggests elderly transplant recipients having a significant survival advantage over similar patients on HD and patients should not be denied transplantation purely on the basis of age (Oniscu et al. 2004).

When comparing CTX and LTX, clinical outcomes are better in LTX. Matas et al. studied survival in TX recipients with 10 years of graft function. The 25-year survival rates in LTX and CTX were 57% and 39%, respectively, and graft survival rates were 43% and 27% (Matas et al. 2008). Similarly, in a Dutch study, after adjustments of covariates, the relative risk of mortality for LTX recipients was half of that (0,5) for CTX. The crude mortality rates, being highest within the first year post-transplantation and decreasing thereafter, were 1,3 and 3,3 per 100 patient-years for LTX and CTX, respectively (Arend et al. 1997).

Survival of grafts has markedly improved during the decades of TX experience and the increase in survival has been mostly attributed to improvements in first-year survival (Lamb et al. 2011). Incidence of acute rejection has decreased and rates lower than 10% have been reported (Hariharan et al. 2000; Matas 2014). First year graft survival in western countries approximates 90% (Lentine et al. 2012; Gondos et al. 2013). Schnitzler et al examined national registry data to investigate associations of renal function at one year posttransplant with clinical outcomes. Their study included over 38 000 transplant recipients in 1995–2003. Estimated

GFR at one year posttransplant was strongly associated with graft failure and mortality in years 4 and 7 (Schnitzler et al. 2011). Previous studies have also reported poor graft function to predict loss of transplant (Hariharan et al. 2002; Kaplan et al. 2003). Compared with reduced graft function, the impact of other conditions on graft and patient survival was much weaker. Delayed graft function and acute rejection predicted graft loss in the first three years and young age and polycystic disease as a cause of ESRD associated with improved graft survival. Existence of diabetes was associated with patient mortality but not with graft loss (Schnitzler et al. 2011).

Compared to the general population, mortality surplus among kidney transplant recipients still exists. In a large registry based study from the United States, relative 10-year survival estimates (observed survival divided by expected survival) indicated excess mortality in all age groups of transplant recipients. The relative survival ranged from 93,5% (age group 0 to17 years) to 57,6% (age over 60 years) for cadaveric kidney recipients and 95,0% to 72,4% for living kidney recipients. The observed 10-year survival rates varied from 94,5% (living kidney recipient aged under 17) to 43,9% (cadaveric kidney recipients over 60 years). Rates were systematically lower than they were among the general population. (Gondos et al. 2011)

2.4 Quality of life in renal replacement therapies

2.4.1 Quality of life in dialysis modalities

Compared with the no-treatment option, dialysis is reasonably effective in sustaining life in the majority of ESRD patients, but its capacity to restore health is much weaker. Patients on dialysis not only face the health problems of chronic renal failure but also the burden and dependence on a time-consuming treatment (Mazairac et al. 2012). Fatigue, lack of energy and itching have been reported the most common symptoms (Laupacis et al. 1992; Merkus et al. 1999) and poor physical functioning (Leaf and Goldfarb 2009; Johansen et al. 2010), depression (Wuerth et al. 2001), sexual dysfunction (Juergense et al. 2001; Finkelstein et al. 2007) and sleep disorders (Kutner et al. 2007; Kutner et al. 2008) are also usual problems among dialysis patients. HRQOL among HD patients has been found to be markedly lower than in the general population (Wight et al. 1998) and it is even

lower than in patients with e.g. congestive heart failure, chronic pulmonary disease or cancer (Mittal et al. 2001). However, the quality of life is a relative concept and results depend on available choices. In his letter to the editor in 1979, Naish reminded that four out of five transplanted recipients gained the life style that they had hoped for and two-thirds of patients in HHD were in full-time employment – at a time when many patients were dying without the referral to the replacement therapy (Naish 1979).

Varied and to some extent contradictory results have been yielded when HRQOL has been compared between PD and HD, depending on the patient characteristics and instruments used (Griva et al. 2013). Mostly, after adjustments or when patient groups have been closely matched, no remarkable differences in HRQOL outcomes have been found (Merkus et al. 1999; Mingardi et al. 1999; Diaz-Buxo et al. 2000; Bakewell et al. 2001; de Wit et al. 2002; Harris et al. 2002; Peng et al. 2010; Griva et al. 2013; Okpechi et al. 2013). Differences emerge in some domains such as physical and sexual functioning outcomes favouring HD (Merkus et al. 1999; Diaz-Buxo et al. 2000; Ginieri-Coccosis et al. 2008) and ability to travel and lower depression in PD (Kalender et al. 2007; Brown et al. 2010; Theofilou 2011), respectively. A similar rate of depressive symptoms among elderly patients has been reported as well (Harris et al. 2002). In a recent South African study HRQOL scores were low in dialysis patients but no significant differences between HD patients and PD patients were found (Okpechi et al. 2013). Contrary to most studies, in a prospective study from the Netherlands, a favorable effect of HD on physical HRQOL over time was found compared with PD, whereas scores for mental HRQOL remained similar (Merkus et al. 1999).

Moreover, compromised HRQOL has been found to independently predict an increased risk of death in dialysis patients (Kalantar-Zadeh et al. 2001; Knight et al. 2003; Mapes et al. 2003; Lopez Revuelta et al. 2004; Unruh et al. 2008; Shiao et al. 2009). In HD patients, physical component summary in the SF-36 questionnaire was as significant a predictor of mortality as was the protein catabolic rate or fractional urea clearance, which commonly are used to measure the efficacy of dialysis treatment and low score also correlated with an increased risk of hospitalization (DeOreo 1997).

In a small Finnish prospective study, 29 patients entered dialysis treatment and their HRQOL was assessed at the initiation of RRT, at six months and at 12 months. Significant improvement in HRQOL was found during the year (Hallinen et al. 2009). However, higher HRQOL scores after initiation of RRT is not definite. Invasive interventions and time commitment are required to maintain

both HD and PD and, especially among elderly patients with several comorbid conditions, rehabilitation is often unsatisfactory (Murtagh et al. 2007). In a prospective UK study, life satisfaction decreased significantly after dialysis initiation among elderly patients whereas it remained stable in patients opting for conservative treatment (no dialysis). Median survival was 1317 days among HD patients and 913 days in conservative treatment. The authors concluded that patients opting for conservative treatment tend to maintain HRQOL but the price may be some reduction in survival. The number of gained life-days on HD compared to conservative treatment seems to be approximately the number of HD sessions (Da Silva-Gane et al. 2012). In a prospective study from Singapore, RRT did not improve quality of life among 101 elderly or patients with high comorbid burden and renal failure compared to those who remained in conservative treatment (Seow et al. 2013). Age alone should not be used as a barrier to treatment; comorbidity is a more important determinant of outcome than age. In a prospective UK study mental HRQOL in dialysis patients aged 70 years or more was similar to that of elderly patients in the general population and (Lamping et al. 2000).

More frequent or nightly dialysis has been shown to provide a better outcome than conventional HD. In a randomized trial, individuals opting for CHD six times per week reported improved physical health compared with patients randomized to three times per week HD (Hall et al. 2012). In another study, patients treated with short daily HD at home, had a significant improvement in scores measuring physical health during a 12 months follow-up (Finkelstein et al. 2012). Similarly, patients on NHD had higher perceived physical health scores and equal mental health scores compared with patients on conventional HD (Cafazzo et al. 2009). McFairlane et al found NHD dominant over conventional HD; overall HRQOL was better and treatment related costs were lower on NHD (McFarlane et al. 2003). A recent randomized trial assigned patients either frequent daily (6-times-weekly) HD, frequent nocturnal (6-times-weekly) HD or conventional (thrice-weekly) CHD. Self-reported mental health improved in frequent daily HD compared with conventional HD but no significant changes were detected in patients on frequent nocturnal HD (Unruh et al. 2013). Some authors have suggested that the HRQOL of dialysis patients may be improved by managing and correcting factors like anaemia and hyperparathyroidism, which have been indicated to be associated with low scores (Okpechi et al. 2013). SatHD has been reported to provide similar, if not better HRQOL compared to CHD (Roderick et al. 2005).

HDF provides more effective removal of waste products than conventional HD does. However, there was no difference in survival between these two modalities in a large randomized trial (Grooteman et al. 2012) and HDF does not seem to improve HRQOL, either. Mazairac et al (Mazairac et al. 2013) examined the effects of HDF versus HD on HRQOL in a prospective study including 714 patients. No significant differences were found. Both parallel (Ward et al. 2000) and HDF favouring (Lin et al. 2001; Kantartzi et al. 2013) results have been reported in smaller studies.

Patients on APD are allowed to receive their fluid exchanges at night-time and time during the day can be spent on other activities. However, a prospective study comparing APD and CAPD did not show major differences in HRQOL between these two modalities after adjusting for differences in patient characteristics and comorbidity (Michels et al. 2011). Previously, compared with CAPD, values in domains for mental health were higher in APD in a smaller study (De Wit et al. 2001). Also in a small Danish study, higher scores in domains for social activities and time for work and family were found in patients on APD than on CAPD whereas scores measuring sleep quality were lower (Bro et al. 1999). In another study, scores on scales reflecting physical processes were worse and those reflecting mental processes were better on APD than on CAPD (Diaz-Buxo et al. 2000). A recent study from Mexico reported significantly better HRQOL on APD compared with CAPD (Cortes-Sanabria et al. 2013).

2.4.2 Quality of life in kidney transplantation

Kidney transplantation is believed to provide considerable improvement in HRQOL when compared with dialysis (Evans et al. 1985). In a prospective study, HRQOL was evaluated in a cohort of dialysis patients before and after transplantation. A significant improvement was found (Russell et al. 1992). In stable wait-listed dialysis patients who received a kidney transplant, HRQOL scores of almost all domains had improved by six months after transplantation compared to scores during pre-transplantation and they remained at about the same level throughout the two-year follow-up (Laupacis et al. 1996). In another study, an improvement in emotional and physical well-being was associated with successful kidney transplantation in patients evaluated before and after the procedure (Park et al. 1996). In a recently published study from Georgia, HRQOL of 120 patients on HD, 43 patients on PD, nine transplant patients with graft failure, 120 healthy age-

and sex-matched controls and 48 transplant recipients of functioning transplant were reported. The mean scores did not differ between controls and TX patients. TX patients also scored significantly higher in all domains than patients on PD and HD. Graft loss was associated with decreased HRQOL (Maglakelidze et al. 2011).

In Finland, Ortiz et al. studied the influence of dialysis modalities on HRQOL before and after TX. The 15D instrument was used in the assessment and altogether 64 dialysis patients who answered the 15D questionnaire were evaluated again after TX. The mean time elapsed between the 15D surveys was 4,5 years and the mean time from transplantation to the second measurement was 3,5 years. During dialysis, the highest HRQOL scores were found in HHD patients and the lowest among patients in CHD. After TX, HRQOL improved significantly in 79% of PD patients, 48% of HHD patients and 54% of CHD patients. On the other hand, 15D scores decreased in 14%, 24% and 23% in patients in PD, HHD and CHD, respectively. The patients treated with CHD and PD benefited the most from TX. The low number of pills and employment were statistically significantly associated with a better HRQOL. (Ortiz et al. 2014)

Kidney transplant failure was found to associate with reduced HRQOL also in a study by Perl et al. In an analysis with data from the Dialysis Outcomes and Practice Patterns Study (DOPPS), 2806 patients wait-listed for TX were compared with 1856 patients with transplant failure. After adjusting for covariates, patients with graft failure reported significantly inferior HRQOL and hazard ratios for mortality and hospitalization were higher. The reduction was largest in patients who had experienced loss of graft within three months representing transitional period as patients have to adapt to loss of autonomy (Perl et al. 2012).

In a large recently published meta-analysis of 110 studies, consistent and clinically relevant improvements in HRQOL associated with TX was found. The vast majority of analyses significantly favored TX over HD whereas none of them favored dialysis. Results seemed to be consistent regardless of variety of settings, they remained after adjustments of covariates and they were observed across broad range of HRQOL instruments. According to the authors, since reduced HRQOL is a hallmark of kidney failure, these improvements may be regarded as the most important advantage of transplantation. (Tonelli et al. 2011)

In another meta-analysis the researchers gathered data from 190 studies including over 56 000 patients with CKD stage 3 to 5 generating 326 utility estimates. Of these, 226 were from patient on dialysis treatment and 66 were from kidney transplant recipients. The highest score on HRQOL (0,82) was found among transplant patients, and utilities in PD and HD were 0,72 and 0,69,

respectively. The difference between PD and HD was not statistically significant. Within PD, higher mean utility was found on APD compared with those on CAPD. Compared to non-diabetics, patient groups with diabetes had lower scores on HRQOL. (Wyld et al. 2012)

2.5 Cost evaluation of renal replacement therapies

In terms of mortality, morbidity and economic costs, CKD is one of the most severe chronic medical conditions (Thamer et al. 1996). The total costs of treating patients with established renal failure requiring RRT approximates to 1–2% of the overall health budget in the UK, which is disproportionately greater than the prevalence of 0,05% of this patient population among the general population (Nicholson and Roderick 2007; Sharif and Baboolal 2012). In Spain of the 7,7% of Gross Domestic Product spent on health care, 1,5% is allocated on ESRD (Luno 2007) and Italy, with 8,3% of its GDP spent on health care, allocates 1,8% on ESRD, respectively (Pontoriero et al. 2007). Similar results have been reported in the Netherlands (De Wit et al. 1998). High costs are largely caused by the expensive technology and equipments and the need for professional labour in the delivery of treatment. In addition, remarkable comorbid conditions contribute to increasing expenditures. In TX patients, costs are induced by the transplantation procedure and related postoperative hospitalization and the need for immunosuppressive medication.

2.5.1 Costs of hemodialysis

In 1969 MacRae et al estimated costs in chronic hemodialysis in the UK (Macrae et al. 1969). In a letter to the editor, they presented a cost of a single treatment session in their hospital (UK Pounds) 9. Another early report from Canada in 1972 (Rae et al. 1972) presented costs of training and treating 22 HHD patients over an 18-month period. The annual maintenance costs were found to be "no more and often less, than those of the institutional care of any other chronic malady". Average cost of keeping a patient at home for a year was (Canadian \$) 3728. In 1975, a British study estimated annual costs (UK Pounds) of 4720 on CHD and 2600 on HHD (Buxton et al. 1975).

Since that treatment costs have been found lower in HHD compared with CHD in several other studies. A multi-centre Canadian study compared CHD, HHD, SatHD and CAPD and costs were lower in HHD (Canadian \$ 32 570) than in CHD (88 585) (Goeree et al. 1995). In France, Jacobs estimated annual costs (US\$) in CHD, HHD and SC-HD at 80 000, 42 000 and 50 000 (Jacobs 1997). Mackenzie and Mactier found costs on a single year on CHD and on HHD (UK Pounds) 15 470 and 13 577, respectively. They also estimated the payback period required to offset higher initial costs for HHD at 14,2 months (Mackenzie and Mactier 1998). Results favouring HHD were also reported in a prospective descriptive survey from Canada. Costs of 33 patients on nocturnal HHD six times per week and 23 patients on CHD three times per week were presented. Even though costs for HD materials were higher in HHD, total annual costs were lower, mainly due to lesser costs in staffing and possibly for hospitalization and medication. Annual costs in CHD and HHD were (Canadian \$) 68 935 and 56 394, respectively (McFarlane et al. 2002). A systematic review published in 2000 identified 25 studies that focused on economic evaluations of hemodialysis in Western Europe. Only four out of 25 met authors' standards for reporting and completeness. Of four studies, all showed that average annual costs of HHD were less than costs on CHD (Peeters et al. 2000).

In Finland, Malmström et al compared costs and HRQOL of HHD and SatHD. Societal perspective was taken and all treatment-related costs including the costs for transportation were taken into account. Compared with SatHD, annual costs for dialysis and hospital treatment were slightly higher on HHD (EUR 31 834 vs. 27 528) but due to lower costs for transportation on HHD, there was no difference in total costs (approximately EUR 39 000). HRQOL scores (measured by 15D instrument) were equal in both modalities (Malmström et al. 2008). In the UK, semi-structured interviews were used to identify steps involved in delivering the different treatment modalities and costs were determined from the provider's perspective. Annual costs in CHD, HHD and SatHD were (UK Pounds) 35 023, 20 764 and 32 669, respectively (Baboolal et al. 2008).

A summary of studies assessing costs of HD is shown in Table 2.

Table 2. Studies assessing costs of hemodialysis

Author	Country Currency	Study type	HD options and costs	Comments
MacRae et al. 1969	UK Pounds	Cost-analysis, estimate	CHD: 9	Costs per single session, solely dialysis costs
Rae et al. 1972	Canada Can\$	Cost-analysis, cohort study	HHD: 3728	Annual dialysis related costs
Buxton et al. 1975	UK Pounds	Cost analysis estimate	CHD: 4720 HHD: 2600	Annual maintenance costs
Goeree et al. 1995	Canada Can\$	Cost analysis Prospective cohort study	CHD: 88 585 HHD: 32 570 SC-HD: 55 593	Production costs, total annual healthcare costs
Jacobs 1997	France US\$	Cost-analysis Estimate	CHD: 80 000 HHD: 42 000 SC-HD: 50 000	Estimated nationwide average costs per patient per year
Mackenzie and Mactier 1998	UK Pounds	Cost-analysis Prospective cohort study	CHD: 15 470 HHD: 13 577	Annual healthcare costs, overhead and transportation excluded
McFarlane et al. 2002	Canada Can\$	Cost analysis Cohort study	CHD: 68 935 HHD: 56 394	Total annual healthcare costs
Malmström et al. 2008	Finland EUR	Cost analysis Cohort study	HHD: 38 477 SC-HD: 39 781	Total annual healthcare costs
Baboolal et al. 2008	UK Pounds	Cost analysis Multicentre cohort study	CHD: 35 023 HHD: 20 764 SatHD: 32 669	Annual dialysis related costs, provider's perspective

2.5.2 Cost-effective and cost-utility analyses of hemodialysis

In a study from the Netherlands a Markov model over five years was created. Both dialysis-related and other health care costs were included and a societal perspective was taken. The model presumed similar survival among dialysis modalities. CHD was the least cost-effective modality whereas HHD and SatHD offered better outcomes with less costs (De Wit et al. 1998). Mohr et al obtained data on the HRQOL and clinical outcomes from more than 60 reports. By applying cost data based on reimbursements in the US, they calculated that daily HD – whether performed in-centre or at home – was less costly than conventional thrice-weekly CHD. They also estimated that, compared with CHD, at least 8% reduction in hospital days is required for daily HHD to be cost saving; a result that actually was

exceeded in referred studies (Mohr et al. 2001). Contrary to those results, in a large survey from the UK, there was no difference either in costs or outcomes between SatHD and CHD (Roderick et al. 2005).

While several studies have found economic advantages in HHD over conventional CHD, less is known about effects of different CHD regimens on treatment costs. Lee et al reported a simulation model which compared effectiveness of varying frequencies and session lengths of CHD. Rather conservative assumptions of the effects of more frequent HD were used. The CER increased with the frequency of CHD and none of the strategies utilizing five weekly sessions achieved an ICER below (US\$) 75 000 and all of those with six weekly sessions had ICER over 125 000. Compared with the common US treatment schedule of 3,5 hours thrice-weekly, ICERs ranged from 112 000 to 1491 000 in a regimen with five 2,5 hours treatment sessions weekly, depending on the estimated values of achieved effects in sensitivity analysis. The authors concluded that, given the considerably increased costs in more frequent CHD, its effects should be dramatically more beneficial to be cost-effective. (Lee et al. 2008)

In their other study, Lee et al made an effort to update the cost-effectiveness of dialysis by using the data from the USRDS and other sources. A simulation model was developed to estimate costs, life expectancy and HRQOL of current dialysis practice relative to scenarios to delay the timing of initiation of dialysis and also the alternative of not start dialysis. In this study, by using current practice to start dialysis (starting dialysis when GFR have dropped below 9 ml/min/1,73 m²), mean survival was estimated to be on average 82 months and number of quality-adjusted life months were 45. By slightly, moderately and significantly delaying the initiation of dialysis, survival decreased to 69, 58 and 51 months, respectively. Patients with a decision to completely withhold dialysis were expected to survive 48 months in this scenario, a figure which hardly is an understatement. Mean lifetime expenditures per patient ranged from (US\$) 135 000 (no dialysis) to 281 000 (current practice). Compared with no dialysis option, ICER (\$/QALY) of current practice was over 110 000. In scenarios of current practice with slight, moderate and significant delay in the initiation of dialysis, ICERs were in between 40 000 to 99 000 compared with no dialysis. (Lee et al. 2009)

A more recent Canadian study compared cost-utility between CHD and nocturnal frequent HHD. A Markov model was generated utilizing data from controlled trials and costs were evaluated from payer's perspective over a lifetime horizon. Nocturnal HHD dominated CHD: Compared with conventional thrice-weekly CHD, frequent nocturnal HHD provided cost savings of (Canadian \$) 6700

and an additional 0,38 QALY. Annual probability of technique failure in nocturnal HHD was set at 7,6% (Klarenbach et al. 2013).

A summary of CEAs and CUAs evaluating HD is shown in Table 3.

Table 3. Studies assessing CE and CU of hemodialysis

Author	Country Currency	Study type	HD options and costs	Comments
De Wit et al. 1998	The Netherlands Dutch Guilders	CEA Simulation model	CHD: 152 666 HHD: 129 456 SatHD: 134 531	Total health care costs, societal perspective. First-year costs
Mohr et al. 2001	USA US\$	CUA Review	CHD HHD Reduction of at least 8% in hospital days is required for HHD to be cost-saving	Data on outcomes from previously published studies, cost data from reimbursements in the USA
Roderick et al. 2005	UK Pounds	CEA Multicentre cohort study	CHD SatHD Similar costs and outcomes	Incomplete costing noted by authors, CE of modalities remains uncertain
Lee et al. 2008	USA US\$	CEA Simulation model	CHD x3/week CHD x5-6/week Frequent CHD not CE	Compared with CHD x3/week, ICERs in all more frequent strategies over \$75 000
Lee et al. 2009	USA US\$	CUA Simulation model	No dialysis CHD, current practice CHD, slight to significant delay in the initiation of therapy	ICERs compared with no dialysis: Current practice 110 814 Slight delay 99 189 Moderate delay 80 993 Significant delay 40 446
Klarenbach et al. 2013	Canada Canadian \$	CUA Simulation model	CHD HHD HHD dominated CHD	Payer's perspective, lifetime horizon. Savings \$6700 and additional QALY 0,38 gained in HHD

2.5.3 Costs of peritoneal dialysis

In 1992 King et al compared costs and rate of complications in 10 patients on APD and 30 patients having CAPD over two years. Dialysis related costs were not reported but, according to the authors, expenses for fluids and disposables were comparable between the groups. In APD, complication rate and costs for treating

complications were lower and all the APD patients who had previous experience in CAPD, preferred APD for its convenience (King et al. 1992).

In a Canadian multicenter cohort study, total annual healthcare costs in CAPD patients were (Canadian \$) 44 790 (Goeree et al. 1995). Provider's perspective was applied. Another Canadian study from the 1990s (Coyte et al. 1996) found matching results in pediatric patients: no remarkable difference in cost between CAPD and APD were found, costs of a typical patient on CAPD and APD were (Canadian \$) 47 569 and 48 658 in a year, respectively. Complication-related costs were not included in these figures. Since that several studies have reported higher costs in APD compared with CAPD. De Wit et al. (De Wit et al. 1998) developed a simulation model assessing total health care costs from a societal perspective. Costs in CAPD and APD were (Dutch Guilders) 102 239 and 129 951, respectively, producing a CAPD to APD cost ratio of 0,79. Studies by Bro et al, Lee et al and Baboolal et al all included solely dialysis related costs and CAPD to APD cost ratios in between 0,72–0,81 were found (Bro et al. 1999; Lee et al. 2002; Baboolal et al. 2008). In a recent study from Mexico, total healthcare costs in 41 patients (22 on CAPD, 19 on APD) were evaluated from a payer's perspective. No significant difference were found, annual direct medical costs (US\$) in CAPD and in APD were 14 798 and 15 389, respectively (Cortes-Sanabria et al. 2013).

A summary of studies assessing costs of peritoneal dialysis is presented in Table 4.

Table 4. Studies assessing costs of peritoneal dialysis

Author	Country Currency	Study type	PD options and costs	Comments
King et al. 1992	UK Pounds	Cost analysis Cohort study	CAPD: 832–1308 APD: 32–108	Annual costs for treating complications. Costs for fluids and disposables "comparable", exact amounts not reported
Goeree et al. 1995	Canada Canadian \$	Cost analysis Cohort study	CAPD: 44 790	Production costs, total annual healthcare costs
Coyte et al. 1996	Canada Canadian \$	Cost analysis Estimation	CAPD: 47 569 APD: 48 658	Pediatric patients, provider's perspective. Estimated annual dialysis-related costs, uncomplicated cases
De Wit et al. 1998	The Netherlands Dutch Guilders	CEA Simulation model	CAPD: 102 839 APD: 129 951	Total annual health care costs, societal perspective. First-year costs
Bro et al. 1999	Denmark US\$	Cost analysis Prospective randomized study	CAPD: 22 265 APD: 27 375	Solely dialysis costs. Originally reported as daily costs
Lee et al. 2002	Canada US\$	Cost analysis Prospective cohort study	CAPD: 14 400 APD: 18 156	Solely dialysis costs. Originally reported as monthly costs
Baboolal et al. 2008	UK Pounds	Cost analysis Multicentre cohort study	CAPD: 15 570 APD: 21 655	Solely dialysis costs, provider's perspective
Cortes-Sanabria et al. 2013	Mexico US\$	Cost analysis Prospective cohort study	CAPD: 14 798 APD: 15 389	Total annual health care costs, payer's perspective

2.5.4 Economic studies comparing hemodialysis with peritoneal dialysis

In 1984, results of a Canadian cost-effectiveness analysis from a payer's perspective were published. This early analysis evaluated health care costs in years 1980–1981 in 44 patients treated with CAPD and HD. In the cost analysis a fully allocated unit cost for each consumed service was applied and overhead costs were included. Costs per life year gained were (Canadian \$) 33 400 for CAPD and 48 700 for HD (Churchill et al. 1984). Prowant et al. recorded cost data on 21 patients on CAPD and 25 patients on CHD in 1986. Total charges for dialysis therapy, renal disease

related hospitalizations and emergency department visits during a 12-month period were evaluated. Total costs (US\$) were significantly less in CAPD (26 453) than in CHD (45 586) (Prowant et al. 1986). In two other US studies from the 1980s, differences between the modalities were insignificant. Both studies measured costs as Medicare allowable charges for medical services and payments for dialysis therapy were based on fixed rates, which were identical for CHD and CAPD (Smith and Wheeler 1988; Smith et al. 1989).

A Brazilian CEA evaluating RRTs was published in 1990. Files of 121 patients who entered in RRT in 1983–1985 were analyzed. Patients with diabetes and arteriosclerotic cardiovascular diseases were excluded. Cost per life-year of survival in CHD and CAPD were (US\$) 10 981 and 12 578 (first year) and 10 065 and 12 134 (second year). Dialyzers were estimated to be reused an average of five times and the authors stated that without reuse of dialyzers the cost per life-year of survival on HD would have risen up to 22 000–24 000 instead of some 10 000 (Sesso et al. 1990). In German, Nebel and Finke reported results of their study comparing costs in HHD, CHD and CAPD patients. Their prospective analysis included altogether 88 dialysis patients having been dialyzed for at least two years. Dialysis related costs and transportation were evaluated. Costs in HHD and in CAPD were close to each other but in CHD costs were 57% higher compared with CAPD (Nebel et al. 1991).

In Finland Varis minutely identified all resource use of health care services in dialysis patients at Tampere University Hospital (Varis 1994). All dialysis patients who entered in RRT in 1982–1987 were included in the study and provider's perspective was taken. 55 patients started on CHD and 39 on CAPD. Costs for the first six months (Finnish Marks) were 118 719 in CHD and 133 126 in CAPD and for the second six months they were 100 014 (CHD) and 106 770 (CAPD), respectively. Also costs for the second year were somewhat lower in HD (210 791) than in CAPD (216 706) (HD to PD cost ratio 0,97) and high CAPD costs which exceeded those reported elsewhere were acknowledged by the author.

A Canadian prospective cohort study evaluated total health care costs in 125 dialysis patients. CHD was almost twice as expensive as CAPD (HD to PD cost ratio 1,97) whereas costs in HHD were much lower comprising only 72% of those in CAPD. Costs in SC-HD were in between costs of CHD and HHD and they were 24% higher than costs in CAPD (Goeree et al. 1995).

In Sweden annual costs (US\$) were estimated at 30 000 in CAPD, 60 000 in CHD and 40 000 in HHD (Karlberg and Nyberg 1995). A UK nationwide estimation assessed reimbursements on the provision of RRT. Average modality

costs in HHD and PD were close to each other (HD to PD cost ratio 0,94) but costs for CHD were 48% higher compared with PD (Haycox and Jones 1996).

In the mid-1990s four different studies reported parallel results with higher costs in CHD compared with PD: Coyte et al. assessed costs in pediatric patients in Canada. Costs (both direct dialysis related expenses and overhead) for typical treatment protocols were evaluated from provider's perspective. In uncomplicated cases, only slight difference between costs in CAPD compared with APD was found but costs in CHD were 56%–60% higher than costs in either CAPD or APD (Coyte et al. 1996). Piccoli and colleagues utilized data from multiple previous studies as they evaluated average costs (US\$) of dialysis in Italy. Costs of 186 per session in CHD and 50 per day in CAPD were applied and an annual CHD to PD cost ratio 1,59 was generated. Costs in APD were over two times higher compared with CAPD in this study (Piccoli et al. 1997). Bruns et al. included 148 US dialysis patients (CHD and CAPD) in their study and costs were measured as annual charges. HD to PD cost ratio 1,52 was found (Bruns et al. 1998). In a study from the Netherlands, a simulation model assessing total healthcare costs from a societal perspective was created and, again, costs in CHD were 48% higher compared with CAPD. Additionally, a short report from the Philippines presented costs over eight years in CHD and CAPD. Details of cost accounting were not reported but a HD to PD cost ratio of 1,14 was found (Naidas et al. 1998).

After the year 2000, Kirby and Vale conducted a CEA of CHD and CAPD in Scotland. In their model, 16 different scenarios were applied to simulate plausible variations in the course of treatment during the first year. Cost analysis included expenses for dialysis, access surgery and managing complications from the provider's perspective. According to the model, survival was slightly better in CHD compared with CAPD. Direct costs for dialysis were close to each other in CHD and CAPD but costs for treating complications were higher in CAPD. CHD dominated (better survival and lower costs) in eight of the 16 different scenarios, and ICERs for CHD were in between (UK Pounds) 4750–40 414 in the other eight scenarios. The authors concluded that, according to their model based upon limited literature, it may be more cost-effective to manage patients with CHD than with CAPD. (Kirby and Vale 2001)

Lee et al published a study evaluating direct health care costs in 332 dialysis patients who had been on therapy longer than six months. Perspective of the purchaser was taken and patients were prospectively followed for 12 months. Overall annual costs (US\$) were 51 252 in CHD and 42 057 in SatHD. Costs in

HHD were lower (29 961) but the number of patients in this modality was only nine. Of 38 PD patients, 32 were on CAPD and six on APD and their costs are analyzed together. Average annual costs on PD were 26 959 (Lee et al. 2002).

In Sweden, Sennfält et al conducted a CUA comprising 68 matched pairs eligible both for HD and PD. Cost analysis included expenses for dialysis, medication, overhead and transportation. Indirect costs were also assessed and calculations were based on estimations of values of lost spare time and working time. Costs per QALY (US\$) were 98 530 and 82 470 for HD and PD. Estimated monthly indirect costs were slightly higher for HD (3493) compared with PD (2355) (Sennfält et al. 2002).

In 2003, a British prospective study assessed costs in dialysis patients aged 70 years and over. A societal viewpoint from the payer's perspective was taken and analysis included costs for medical and social services. Privately borne costs were taken into account. Only marginal and statistically insignificant difference in costs between HD and PD were found, costs were 11% higher in CHD compared with PD (Grun et al. 2003).

In Turkey, all health-care expenditures for 104 dialysis patients over a two-year period were collected in 2004. No difference between the modalities was found, HD to PD cost ratio was 1,02 (Erek et al. 2004). In 2005, Shih et al analyzed register data on 3423 incident dialysis patients in the United States. After adjustment of patient characteristics, reimbursements (US\$) were approximately 20% higher in CHD (68 253) compared with PD (56 807), a difference being statistically significant. Modality switches were found to increase expenditures (Shih et al. 2005).

Data on use of the healthcare services in a historical cohort 30 CHD patients and 30 CAPD patients in several centres in Malaysia were collected. Cost data included expenses on dialysis and dialysis-related medications. Overhead costs were taken into account. In CHD, direct costs for dialysis were lower and costs for infrastructure and staff were higher than in CAPD. The number of life years saved was 10,96 for CHD and 5,21 for CAPD. Costs per life-year saved (Malaysian Ringgits) were nearly equal between modalities: 33 642 for CHD and 31 645 for CAPD (Hooi et al. 2005).

Pacheco et al. conducted a CUA including a historical cohort of 159 dialysis patients from five units in Chile. 102 of them were on CHD and of 57 patients on PD, 50 were on APD. Patient characteristics did not significantly differ between the groups and HRQOL indexes (SF-36) were practically similar (65,75 for CHD and 66,88 for PD). Direct global health-care costs (US\$, measured as

reimbursements) were slightly higher for CHD than for PD (14 884 vs. 16 666). The authors also estimated the amount of indirect costs induced by loss of productivity and unemployment at 5 508 for CHD and 4 061 for PD. After addition of indirect cost to direct costs, no significant difference in total costs between the modalities was found and the authors concluded that CHD and PD show similar cost-utility in their country. (Pacheco et al. 2007)

In Japan, annual charges reimbursed by for HD and PD were (US\$) 35 914 and 41 910 in a nationwide survey. Costs for hospitalization were included (Fukuhara et al. 2007). In Thailand, a Markov model was conducted to evaluate the CU of CHD and CAPD over palliative care. Total health care costs from the provider's perspective and also indirect costs were included in the analysis. Patient aged 20–70 years and lifetime costs were evaluated. Compared with palliative care, ICERs (US\$/QALY) in CHD and CAPD were 63 000 and 52 000. Providing treatment in younger patients resulted in a significant improvement in survival and a gain in QALYs (Teerawattananon et al. 2007).

In Europe, the average costs (based on reimbursements) were estimated at US\$ 57 354 for all dialysis modalities in Germany in a year. Definite figures for HD or PD were not presented (Kleophas and Reichel 2007). In a Croatian study presenting the state of RRT in the country, annual reimbursements (US\$) were reported some 26 000 for CHD and 17 000 for PD, respectively (Cala 2007). In the UK, Baboolal et al. evaluated costs in dialysis patients from provider's perspective. They determined the treatment pathways for the different forms of dialysis and the resources used for each of these pathways and costing process took the viewpoint of providers. Semi-structured questionnaires were used to identify steps involved in delivering the treatment over the course of time in individual patients. Dialysis related costs and cost for transportation and medication were taken into account. Costs (UK Pounds) in CHD, SatHD, HHD, APD and CAPD were 35 023, 32 669, 20 764, 21 655 and 15 570, respectively. Costs for CHD were 2,25-fold compared with CAPD and expenditures in HHD and APD were close to each other (Baboolal et al. 2008).

Berger et al. utilized health insurance database in the US to identify 463 patients who had entered into dialysis treatment in 2004–2006 and had been treated for at least 12 months. By using predetermined propensity scoring to control patient characteristics, 50 matched HD–PD pairs were found. Total health care costs (from payer's perspective) were evaluated over a 12-month period. The CHD patients were significantly more likely to be hospitalized and costs in CHD were 33% higher than costs in PD (Berger et al. 2009).

In a review article focusing on peritoneal dialysis in Africa, estimates on costs for dialysis in several sub-Saharan countries were reported. Figures were based on personal communication from leading nephrologists in particular countries and amounts refer to direct dialysis-related costs. Detailed analysis was not provided, but costs (US\$) ranged from 7000 to 24 500 for CHD and 11 500 to 24 500 for CAPD (Abu-Aisha and Elamin 2010). In another article from Egypt, costs for CHD and CAPD (US\$) were estimated at 3120 and 14 600 (Mahmoud et al. 2010). A Nigerian study reported single centre experiences in symptomatic renal failure over a 19-year period 1989–2007. Of a total of 760 patients, RRT was offered for 565 patients (CHD in 556 cases and CAPD in 9 cases). Average annual dialysis-related costs (US\$) in CHD and CAPD were estimated at 20 280 and 29 200. Most of the patients could not meet the expense for the treatment and the median survival after diagnosis for all patients was only two weeks (Arogundade et al. 2011). In India, due to limited health insurance coverage, costs for RRT are paid by patients. Jeloka et al evaluated dialysis-related costs (dialysis, supplies, medication and transportation) in 35 patients on HD and PD. The lower costs for dialysis among HD patient were compensated by higher costs in erythropoietin and transportation and no difference was found in total costs (Jeloka et al. 2012).

Recently, a register-based nationwide survey analyzed costs in dialysis patients in Spain. Costs were measured from a payer's perspective. Total healthcare costs (EUR) and also costs for transportation and indirect costs caused by decreased productivity and early retirement and unemployment were included in the analysis. Direct costs per patient were 37 968 in HD and 25 826 in PD. Based on average salaries, retirement rates and mortality rates, it was considered that 28% of patients on PD, 13% of patients on HD and 46% of those who had received a transplant, continued working. The mean indirect costs were estimated at (EUR) 8029 on HD, 7429 on PD and 5483 in patients with a functioning transplant (Villa et al. 2011). In Brazil, De Abreu et al. assessed cost data on altogether 477 stable dialysis patients from a societal perspective. Of them, 228 patients were on PD. Data were collected over 12 months by using standard questionnaires. The mean annual costs (US\$) were 28 570 for HD and 27 158 for PD. (De Abreu et al. 2013)

Olsen et al (Olsen et al. 2010) applied a Markov model using Danish cost estimates and clinical parameters to evaluate costs over a 10-year period. They found that increasing the number of patients on outgoing treatment (PD, HHD) from 70% to 71% will lead to (EUR) 9,6 million savings (constituting 0,6% of the total dialysis costs) and they concluded a higher percentage of patients on outgoing treatment reducing costs in the future. In an Austrian simulation in 2011 the

authors compared costs, survival and quality of life in HD, PD and TX. Data on costs and transition probabilities were drawn from local registries and a payer's perspective was taken. Most HD patients in Austria are treated with CHD and PD patients with APD and cost data represents these particular modalities. Also non-renal costs and costs for transportation were included in the analysis. The mean first 12 months costs (EUR) for CHD and APD were 43 600 and 25 900, the second year costs were 40 000 and 15 300 and during the third year they were 40 600 and 20 500. By comparison, costs for TX after two years were 12 900 in a year. The authors concluded that by increasing the allocation of PD from a current 7% to 20%, 26 million EUR could be saved and 839 QALYs were gained over ten years (Haller et al. 2011).

Table 5 summarizes economic studies comparing HD and PD.

Table 5. Economic studies comparing hemodialysis and peritoneal dialysis

Author	Country Currency	Study type	Dialysis options and annual costs	Ratio HD/PD	Comments
Churchill et al. 1984	Canada Canadian \$	CEA Cohort study	CHD: 48 700 CAPD: 33 400	1,46	Payer's perspective Direct health care costs, overhead costs included
Prowant et al. 1986	USA US\$	Cost analysis Cohort study	CHD: 45 586 CAPD: 26 453	1,72	Payer's perspective. Non-renal costs excluded
Smith and Wheeler 1988	USA US\$	Cost analysis Register study	CHD: 23 344 CAPD: 21 429	1,10	Payer's perspective, Medicare allowable charges
Smith et al. 1989	USA US\$	Cost analysis Register study	CHD: 23 470–27 463 CAPD: 22 753–29 435	0,93–1,03	Payer's perspective, estimated annual charges
Sesso et al. 1990	Brazil US\$	CEA Cohort study	CHD: 10 981–10 065 CAPD: 12 578–12 134	0,87–0,82	Payer's perspective, cost for two years. Dialyzers and blood line sets reused x 5
Nebel et al. 1991	Germany German mark	Cost analysis Cohort study	CHD: 67 458 HHD: 44 820 CAPD: 42 924	1,57 (CHD) 1,03 (HHD)	Payer's perspective, dialysis related and transportation costs
Varis 1994	Finland Finnish mark	Cost analysis Cohort study	CHD: 210 791 CAPD: 216 706	0,97	Provider's perspective, total annual costs. Year 2

Goeree et al. 1995	Canada Canadian \$	Cost analysis Cohort study	CHD: 88 585 SC-HD: 55 593 HHD: 32 570 CAPD: 44 790	1,97 (CHD) 1,24 (SC-HD) 0,72 (HHD)	Provider's perspective, total health care costs.
Karlberg and Nyberg 1995	Sweden US\$	Cost analysis	CHD: 60 000 HHD: 40 000 CAPD: 30 000	2,00 (CHD) 1,33 (HHD)	Estimated annual costs
Haycox and Jones 1996	UK Pounds	Cost analysis Nation-wide estimate	CHD: 26 266 HHD: 16 794 PD: 17 788	1,48 (CHD) 0,94 (HHD)	Payer's perspective, reimbursements for dialysis therapy
Coyte et al. 1996	Canada Canadian \$	Cost analysis Treatment protocol-based calculations	CHD: 76 023 CAPD: 47 569 APD: 48 658	1,60 (CAPD) 1,56 (APD)	Pediatric patients, provider's perspective. Dialysis-related costs
Piccoli et al. 1997	Italy US\$	Cost analysis	CHD: 29 016 CAPD: 18 250 APD: 40 206	1,59 (CAPD) 0,72 (APD)	Provider's perspective, dialysis related costs. Originally reported as costs per day or session
Bruns et al. 1998	USA US\$	Cost analysis Register study	CHD: 68 891 CAPD: 45 420	1,52	Payer's perspective, single-center study. Annual charges
De Wit et al. 1998	The Netherlands Dutch guilders	CEA Simulation model	CHD: 152 666 CAPD: 102 839 APD: 129 951	1,48 (CAPD) 1,17 (APD)	Societal perspective, total health care cost, year 1
Naidas et al. 1998	Philippines Philippine peso	Cost analysis Cohort study	CHD: 3 966 884 91 CAPD: 3 487 089 93	1,14	Perspective uncertain. Cost for eight years
Kirby and Vale 2001	UK (Scotland) Pounds	CEA Markov modelling	CHD 9924–11076 CAPD 10 860 HD dominates in 8 scenarios, ICER 4750– 40414 for HD in 8 scenarios	0,91–1,01	Provider's perspective. Costs for dialysis, access nursing, and complications. 16 different scenarios.
Lee et al 2002	Canada Canadian \$	Cost analysis Cohort study	CHD: 51 252 SatHD: 42 057 HHD: 29 961 PD: 26 959	1,90 (CHD) 1,56 (SatHD) 1,11 (HHD)	Payer's perspective, treatment-related costs,
Sennfält et al. 2002	Sweden US\$	CUA Cohort study	HD: 98 530 PD 82 470	1,19	Payer's perspective, costs/QALY. Indirect costs estimated
Grun et al. 2003	UK Pounds	Cost analysis Multicenter cohort study	CHD: 26 098 PD: 23 543	1,11	Elderly patients, payer's perspective. Results originally reported as daily costs
Erek et al. 2004	Turkey US\$	Cost analysis Multicenter cohort study	HD: 22 759 PD: 22 350	1,02	Provider's perspective. Total health-care costs

Shih et al. 2005	USA US\$	Cost analysis Register study	CHD: 68 253 PD: 56 807	1,20	Payer's perspective, costs after adjusting patient characteristics
Hooi et al. 2005	Malaysia Malaysian Ringgits	CEA Multi-center cohort study	CHD: 33 542 CAPD: 31 635	1,06	Payer's perspective, renal costs included. Life-years saved 11,0 for CHD and 5,2 for CAPD
Pacheco et al. 2007	Chile US\$	CUA Multi-center cohort study	CHD: 20 803 PD: 20 742	1,00	Payer's perspective, dialysis-related and hospitalization costs. Costs for loss of productivity included, HRQOL measured
Fukuhara et al. 2007	Japan US\$	Cost analysis Register study	CHD: 42 098 PD: 49 215	0,86	Nationwide survey, annual charges. Costs for dialysis and medication
Teerawattananon et al. 2007	Thailand US\$	CUA Markov model	CHD: 63 000 CAPD: 52 000	1,21	Provider's perspective. ICERs (US\$/QALY) compared with palliative care
Kleophas and Reichel 2007	Germany' US\$	Cost analysis	57 354 for all dialysis modalities		Payer's perspective, nationwide annual reimbursements
Cala 2007	Croatia US\$	Cost analysis	CHD: 26 000 PD: 17 000	1,53	Payer's perspective, Estimated average reimbursements
Baboolal et al. 2008	UK Pounds	Cost analysis Multicenter cohort study	CHD: 35 023 SatHD: 32 669 HHD: 20 764 APD: 21 655 CAPD: 15 570	0,96–2,25 (HHD:APD) – (CHD:CAPD)	Provider's perspective Dialysis related costs, medication and transportation. 12 months follow-up
Berger et al. 2009	USA US\$	Cost analysis Cohort study	CHD: 173 507 PD: 129 997	1,33	Payer's perspective. 50 matched HD–PD pairs, healthcare costs over 12 months
Howard et al. 2009	Australia Australian \$	Cost estimate Markov model	CHD: 82 764 HHD: 44 739 SatHD 48 630 CAPD: 56 828	1,45 (CHD) 0,78 (HHD) 0,85 (SatHD)	Payer's perspective. Costs presented alongside CEA of increasing TX and HHD
Abu-Aisha and Elamin 2010	South Africa US\$	Cost analysis	HD: 7 000 PD: 12 000	0,58	Payer's perspective. Costs for solely dialysis treatment, estimate
Abu-Aisha and Elamin 2010	Kenya US\$	Cost analysis	HD: 16 000 PD: 12 000	1,33	Payer's perspective. Costs for solely dialysis treatment, estimate

Abu-Aisha and Elamin 2010	Sudan US\$	Cost analysis	HD: 10 500 PD: 11 500	0,91	Payer's perspective. Costs for solely dialysis treatment, estimate
Abu-Aisha and Elamin 2010	Senegal US\$	Cost analysis	HD: 27 000 PD: 19 500	1,38	Payer's perspective. Costs for solely dialysis treatment, estimate
Abu-Aisha and Elamin 2010	Namibia US\$	Cost analysis	HD: 24 500 PD: 24 500	1,00	Payer's perspective. Costs for solely dialysis treatment, estimate
Olsen et al. 2010	Denmark EUR	Cost analysis Markov model	Increasing number of patients on PD and HHD from 70% to 71% saves EUR 9,6 million/year	-	Payer's perspective, nation-wide estimation
Mahmoud et al. 2010	Egypt US\$	Cost analysis	HD: 3 120 PD: 14 600	0,21	Payer's perspective. Costs for solely dialysis treatment, estimate
Villa et al. 2011	Spain EUR	Cost analysis Register study	HD: 46 897 PD: 33 255	1,41	Nation-wide estimate of total healthcare costs, payer's perspective. Indirect costs included
Haller et al. 2011	Austria EUR	CUA Markov model	CHD: 43 600 APD: 25 900	1,68	Provider's perspective. Total healthcare costs, first year
Arogundade et al. 2011	Nigeria US\$	Cost analysis	CHD: 20 280 PD: 29 200	0,69	Payer's perspective. Costs for solely dialysis treatment
Jeloka et al. 2013	India Rupees	Cost analysis	CHD: 29 252 CAPD: 28 763	1,02	Payer's (patient's) perspective. Monthly out-of-pocket costs for dialysis, medication and transportation
De Abreu et al. 2013	Brazil US\$	Cost analysis Cohort study	CHD: 28 570 PD: 27 158	1,05	Provider's perspective, healthcare costs over 12 months

2.5.5 Costs for kidney transplantation

In 1976, Schippers and Kalff compared cost between CTX and CHD from the payer's perspective. Costs for renal transplantation and subsequent 12 months (Dutch Guilder) were over 44 000 whereas costs for one year of CHD were estimated to require some 65 000, respectively. After the first year, costs of treatment of a patient with a well-functioning graft did not normally exceed 8000 and the authors concluded that these figures demonstrated the enormous economic advantage of kidney transplantation over chronic HD (Schippers et al.

1976). In another study from the 1970s, direct costs and outcomes in 466 transplantation patients in a single centre in the United States were analyzed. The first year costs with a functioning graft were calculated on average at (US\$) 10 519 per patient but, if the course was complicated, the mean costs ranged up to 21 000. Costs for the second year were on average 1120. Two-year survival rates were 100% for recipients of a transplant from a living related donor and 84% for those of a transplant from a cadaver (Salvatierra et al. 1979).

A Belgium study found the one-year mean direct medical costs for TX patients to be EUR 39 827. For patients who had acute rejection and other complications, costs and number of days in hospital were higher compared with those with no rejection (Chaib-Eddour et al. 2005).

Barnieh et al compared costs between CTX and LTX. In this Canadian study, all treatment-related cost information of 357 recipients was collected. 227 patients received a CTX and 130 patients a LTX. Costs were similar: the mean 2-year-costs (Canadian \$) were some 118 000 for recipients of LTX and 121 000 for those of CTX. Due to the limited follow-up, difference in graft survival between the groups was not found but the authors speculated that, given the superior long-term survival for LTX, costs might become lower in LTX recipients compared with those who received a CTX. (Barnieh et al. 2011)

In 2011, average national social insurance program (Medicare) expenditures (US\$) for TX patients were 32 922 in a year. Costs for HD and PD were 87 945 and 71 630, respectively. In patients who had received their transplant within a year, annual inpatient and outpatient costs exceeded 99 000 whereas for patients who had received their graft during preceding years costs were some 12 000. (Collins et al. 2013)

Considerable direct costs are associated with the transplantation procedure. Surgery, procedure-related hospitalization, immunosuppressive medication and close outpatient monitoring cause accumulating of expenditures during the first posttransplant year. In a French study, the average cost of a hospital stay for kidney transplantation were evaluated at EUR 14 100 and the mean length of stay in hospital was 19,4 days (Chaumard et al. 2008) whereas in the US, the hospital charges of transplantation procedure (deceased donor) ranged from US\$ 47 000 to over 72 000. Utilization of expanded criteria donors and donation after cardiac death was applied in this study (Saidi et al. 2007). A figure of US\$ 81 330 was used by Lee et al as cost for transplantation in their simulation model (Lee et al. 2006). In a Chinese study, average charges of living donor kidney transplantation were US\$ 10 531, of which 69% was for medications and 13% for surgical procedures

(Zhao et al. 2012). In highly sensitized recipients, desensitization protocols including immunoadsorption, plasmapheresis intravenous immunoglobulin and antibodies are needed. Despite costly therapies, TX in those patients provided cost-savings during the average four-year follow-up compared to CHD (Al-Jedai et al. 2012).

Summary of economic studies evaluating TX is presented in Table 6.

2.5.6 Economic studies comparing kidney transplantation with dialysis therapies

Kidney transplantation is generally seen as the most cost-effective treatment option of RRT. Sesso et al studied cost-effectiveness of dialysis therapies and TX in Brazil. Total treatment costs were calculated and the payer's perspective was taken. After two years, the costs per year of survival were some (US\$) 7000 for CTX and 3000 for LTX, whereas they were over 12 000 on CAPD and over 10 000 on CHD, respectively. However, survival of patients was better on dialysis therapies compared with TX in this study. The data derive from the 1980s and cyclosporine treatment was not used in these patients (Sesso et al. 1990).

In his thesis in 1994, Varis examined cost of life-months gained by different RRT modalities in Finland. Of 103 incident adult ESRD patients who entered dialysis therapy in 1982–1987, 44 patients received a CTX while others continued dialysis. All treatment-related costs were collected. In TX patients costs for the first six posttransplant months were (Finnish Marks) on average 166 724 and after that they declined markedly being 56 470–66 793 during the second and third year. On HD and PD costs remained rather stable. For the first six months they were some 119 000 on HD and 133 000 on PD. Compared with TX, the second and third year costs were significantly higher on dialysis therapies ranging from some 211 000 to 350 000. (Varis 1994)

In 1996 Laupacis et al reported results from a prospective cohort study which assessed the cost-utility of TX compared with dialysis therapies. 168 dialysis patients on the transplant waiting list were included in the study. In determining costs, resource use of health care services was recorded and a societal perspective was taken. By six months after TX, the mean HRQOL scores had significantly improved compared to pre-transplantation. The mean annual costs of dialysis (Canadian \$) were over 66 000 and the average costs of the first year after TX were identically also over 66 000. After the first year, the second year costs decreased

markedly being about 40% of costs of the first year. In patients who experienced a rapid graft failure, costs during the first year were twice of those of patients with a functioning graft and during the second year they remained about 10 000 higher than they had been on dialysis before TX. (Laupacis et al. 1996)

A report from Taiwan described a retrospective cost assessment comparing HD and CTX. All medical costs (measured as reimbursements) for 75 transplant recipients were collected. Both pre- and posttransplant follow-up was included in the analysis. The average costs for CHD were estimated at (US\$) 25 150 per year and the initial hospitalization costs for a transplantation procedure were 17 500 and charges for outpatient visits and medication were 757 per month thereafter. The high initial costs for CTX were balanced during subsequent months and the total cumulative costs for CHD and CTX were equal at 18 months, CTX being less costly thereafter. The authors suggested that each CTX induced over 106 000 savings in 17 years (predicted maximum graft survival) compared with CHD. (Hu et al. 1998)

Jassal et al examined cost-utility of TX in the elderly. In this study, a model was generated to compare kidney transplantation with continued CHD. Patients, a theoretical cohort of stable patients aged 60 years or more, had no contraindications for TX. Medicare reimbursements were used to estimate costs and transition probabilities between different health states were derived from the literature. Annual cost (US\$) estimates of 50 829 for dialysis and 15 819 for transplantation follow-up were applied. Costs for transplantation surgery were estimated at 64 917. Both CTX and LTX increased life expectancy in all age groups (60–85 years) but only by 8–19 months, depending on the recipient's age and time on the waiting list. Contrary to studies with younger patients and cost-savings associated with TX, in this study costs were higher in TX patients compared with those who continued on dialysis. Cost-effectiveness strongly depended on patient characteristics and on waiting time. In 65-year old patients TX produced 0,2–2 QALYs depending on waiting time and comorbidities. Compared with continuing dialysis, ICERs varied from 14 910 (no waiting time, no diabetes or cardiovascular disease) to 198 609 (two-year waiting time, diabetes and cardiovascular disease). For a 85-year old otherwise healthy patient with four year waiting time ICER was over 14 000 000 (Jassal et al. 2003). In a Turkish study including 135 TX patients (107 from a living donor, 28 from a cadaveric donor 28), the first year costs were (US\$) 23 393, a figure which was equal for costs in HD and PD in the same study. The second year costs declined to 10 028 (Erek et al. 2004).

Several Markov models have been conducted to assess CE in RRT. In an Australian study published in 2009, two nationwide changes from the current practice were modelled: increasing TX by between 10% and 50% in five years and utilizing home-based dialysis (HHD and PD) to the highest rates observed in Australian centres. By determining costs, payer's perspective was taken. Data on patient characteristics and outcomes derived from local registries. Based on these data, considerable advantages were achieved. Up to 26 million savings (Australian \$) and additional 658 QALYs were gained in five years by increasing TX by 50%. Utilizing home-based dialysis more effectively resulted in 122 million savings in five years. (Howard et al. 2009)

Another simulation from Austria utilized data from local registries to assess CE in RRT. Costs in the first posttransplant year for LTX and CTX patients were (EUR) 50 900 and 51 000, respectively. The second year costs were 17 900 and third year costs 12 900 for both LTX and CTX. According to the model, increasing renal transplants from living donors to 10% instead of current 0,1% would provide 38 million savings and 2242 QALYs could be gained over the next ten years and the authors recommended promotion of preemptive TX from a fiscal as well as medical point of view. (Haller et al. 2011)

In a Spanish nation-wide survey, first-year costs (EUR) for TX were 38 313 and 6283 in subsequent years. Payer's perspective was applied (Villa et al. 2011). A single-centre study from Portugal recorded all resource use of health services of 90 TX patients. Costs were measured as reimbursements. Annual costs were (EUR) 61 658 in the first year and 6 526 after that. Costs for both HD and PD were some 28 000. The authors concluded that the break-even point for equal cumulative cost between dialysis and TX occurs at 32 months, thereafter TX is less expensive (Rocha et al. 2012).

Based on registry data from Australia and New Zealand, a two-arm Markov model was created to evaluate the cost-effectiveness of cadaveric kidney transplantation compared with dialysis. The model included two groups of hypothetical potential transplant recipients aged from 25 to 60 years with and without comorbidities. Patients on the one arm were placed on the transplant waiting list whereas patients on the other arm were to remain in dialysis. The progression of each individual through the model was dependent on the age-specific transition probabilities from one health state to another and the entire lifetime of an individual was modelled. An annual discount rate of 5% was employed. Probability of receiving a transplant varied depending on age between 0,148 (18–24 years) and 0,005 (over 75 years) in a year. Age-specific probabilities

for graft failure, mortality and cardiac events were applied. The extent of survival advantage in waitlisted patients was dependent on the underlying characteristics, with the youngest and healthiest gaining the greatest number of incremental life years. However, also the oldest waitlisted patients with cardiovascular diseases and diabetes achieved incremental 0,5 years compared with those who remained in dialysis. In 25-year old patients with no comorbidities, placing in waitlist produced savings of (Australian \$) 16 272 and 3,84 life-years were gained compared to chronic dialysis treatment. In older patients, ICERs (\$/life-year saved) varied from 8 965 to 40 915. (Wong et al. 2012)

Summary of studies comparing TX with dialysis modalities is shown in Table 6.

Table 6. Economic studies evaluating kidney transplantation and comparing transplantation with dialysis therapies

Author	Country Currency	Study type	Results Annual costs	Ratio TX/dialysis	Comments
Schippers et al. 1976	The Netherlands Dutch Guilder	Cost analysis Cohort study	TX, Year 1 45 000 Years 2– CHD 8 000 65 000	0,69 (Year 1) 0,12 (Year 2–)	Direct costs, payer's perspective. Costs for well-functioning grafts
Salvatierra et al. 1979	USA US\$	Cost analysis Cohort study	Year 1 10 519 (no complications) Year 1 21 000 (complications) Year2 1120	–	Annual costs for two years of graft function
Sesso et al. 1990	Brazilia US\$	CEA Cohort study	CTX 6 978 LTX 3 022 CHD 10 065 CAPD 12 134	0,25–0,69	Payer's perspective, cost for two first years. Cost per year of survival
Varis 1994	Finland Finnish Marks	Cost analysis Cohort study	TX 56 470 CHD 210 791 CAPD 216 706	0,27 (TX/HD) 0,26 (TX/PD)	Provider's perspective, total annual costs. Year 2
Laupacis et al. 1996	Canada Canadian \$	CUA Cohort study	TX, Year 1 66 290 Year 2 27 875 Dialysis 66 782	0,99 (Year 1) 0,42 (Year 2)	Societal perspective, total healthcare costs. Prospective study including pre- and post-transplant period
Hu et al. 1998	Taiwan US\$	Cost analysis Cohort study	TX, Year 1 26 584 Year 2– CHD 9 084 25 150	1,05 (Year 1) 0,36 (Year 2)	Payer's perspective. Prospective study including pre- and post-transplant period

Jassal et al. 2003	USA US\$	CUA Markov modelling	65-year old patients, TX compared with CHD. TX produces 0,2–2 QALYs, ICERs 14 910–198 609 (\$/QALY)	–		Payer's perspective (Medicare expenditures). ICERs for TX depended on waiting time and comorbidities
Erek et al. 2004	Turkey US\$	Cost analysis Cohort study	TX, Year 1 23 393 Year 2 10 028 CHD 22 759 CAPD 22 350	1,02–1,05 (Year 1) 0,44–0,45 (Year 2)		Perspective uncertain
Chaib-Eddour et al. 2005	Belgium EUR	Cost analysis Cohort study	Year 1 39 827	–		Payer's perspective. Total healthcare costs
Howard et al. 2009	Australia Australian \$	CEA Markov modelling	Increasing TX by 50% from current practice, saves 26 million and increases 658 QALY	–		Payer's perspective. Nationwide estimate 2005–2010
Haller et al. 2011	Austria EUR	CEA Markov modelling	TX Year 1 51 000 Year 2 17 200 HD 43 600 PD 25 900	Year 1 1,17 (TX/HD) 1,97 (TX/PD) Year 2 0,39 (TX/HD) 0,66 (TX/PD)		Payer's perspective. Increasing renal transplants from living donors to 10% saves EUR 38 million and produces 2242 QALYs over ten years
Villa et al. 2011	Spain EUR	Cost analysis Register study	TX Year 1 38 313 Year 2– 6 238 HD 37 968 PD 25 826	Year 1 1,01 (TX/HD) 1,48 (TX/PD) Year 2 0,16 (TX/HD) 0,24 (TX/PD)		Payer's perspective. Nationwide survey, direct costs
Barnieh et al. 2011	Canada Canadian \$	Cost analysis Cohort study	CTX 121 121 LTX 118 347	–		Two-year costs. Total healthcare costs, perspective uncertain
Rocha et al. 2011	Portugal EUR	Cost analysis Cohort study	TX Year 1 61 658 Year 2– 6 526 Dialysis 28 033	2,19 (Year 1) 0,23 (Years 2–)		Payer's perspective. Direct healthcare costs
Wong et al. 2012	Australia Australian dollars	CEA Markov modelling	Patients aged 25 years: TX saves costs and produces QALYs, Middle-aged to older: ICERs (\$/QALY) 8 965–40 915	–		Waitlisted patients compared with remaining on dialysis, entire life-time evaluated
Collins et al. 2013	USA US\$	Cost analysis Register study	TX 32 922 HD 87 945 PD 71 630	0,37 (TX/HD) 0,46 (TX/PD)		Payer's perspective (Medicare expenditures)

2.5.7 Pre-emptive kidney transplantation and economic aspects

While the economic advantage gained by TX is dependent on the waiting time, TX without preceding dialysis (pre-emptive TX) may be cost-saving. In a short report from the Philippines, a historical cohort of 183 ESRD patients was followed up to eight years. Eight patients underwent a pre-emptive TX. Compared with dialysis patients and those who received their transplant after dialysis period, lower risk of death and lower treatment costs were found in pre-emptive TX (Naidas et al. 1998). Several studies have provided data of lower post-transplant mortality with pre-emptive TX compared with TX after initiating dialysis (Meier-Kriesche et al. 2000; Meier-Kriesche and Kaplan 2002; Goldfarb-Rumyantzev et al. 2005; Huang and Samaniego 2012). Also, the longer the pretransplant dialysis duration, the higher is posttransplant mortality (Helanterä et al. 2014). Dialysis up to six months did not significantly worsen survival but after that mortality increased progressively (Meier-Kriesche et al. 2000). Duration of dialysis was also found to be associated with an increased risk of delayed graft function after CTX (Keith et al. 2008).

2.5.8 Reduced graft function and graft failure

Reduced graft function has been found to impact on costs. In a North American study, association of estimated glomerular filtration rate (eGFR) at one year posttransplant with reimbursements among kidney transplant recipients in 1995–2003 were examined. Average second and third year payments were some (US\$) 9800 and 6400, respectively. In a multivariate analysis, compared with patients with relatively good graft function (eGFR over 60 ml/min/1,73 m²), moderately (eGFR 30–44 ml/min/1,73 m²) and markedly (eGFR 15–30 ml/min/1,73 m²) impaired function were associated with 1 555 and 5 352 higher treatment costs in the second year posttransplant. Graft failure resulting in return to dialysis increased costs by some 48 000 and existence of diabetes was associated with over 14 000 higher costs compared with non-diabetics (Schnitzler et al. 2011).

2.5.9 Distribution of costs in renal replacement therapies

Dialysis treatment in itself is the most important cost-producing factor in HD and PD. In a Canadian study, costs for dialysis treatment were 62% of total costs on CHD and 71% on CAPD, respectively (Goeree et al. 1995). In a UK study

including 171 dialysis patients aged over 70, no significant difference in costs between HD and PD were found. Payer's perspective was applied and costs for medical and social services were taken into account. Dialysis treatment accounted for 69% of costs, medication and hospitalization were the second and third largest items, 12% of costs each (Grun et al. 2003). Bruns et al evaluated dialysis patients' total treatment costs in 1998. In their single-center study, payer's perspective was taken. Average annual costs for treating ESRD were (US\$) 68 891 on HD and 45 420 on PD. Of total costs, 38% and 30% were caused by dialysis treatment on HD and PD, respectively. Hospitalization accounted for 37% to 40% of total costs. They also noted that costs accumulated in certain patients: 25% of patients caused 50% of all costs (Bruns et al. 1998). The same authors reported that a simple comorbidity scale strongly predicted risk of hospitalization, length of hospitalization, mortality and inpatient costs in dialysis patients (Beddhu et al. 2000).

In a Canadian prospective study, dialysis costs accounted for 52% of total costs in CHD patient and 46% in PD patients. Costs for medication were the second largest followed by inpatient (hospitalization) costs (Lee et al. 2002). First-year post-dialysis initiation costs (measured as Medicare reimbursements) in incident dialysis patients over 67 years were found to increase from almost (US\$) 82 000 in 1995 to over 113 000 in 2005. However, after adjustment for inflation, costs were fairly stable over the years. Inpatient costs and outpatient costs both accounted for about 35% of total costs. In Japan, where TX is rare mostly for cultural reasons and 96% of dialysis patients are treated with HD, estimated annual charges for HD and PD were (US\$) 42 098 and 49 215. Dialysis accounted for 83% and hospitalization for 13% of costs in both modalities (Fukuhara et al. 2007).

In 2010, Medicare payments per person per year were (US\$) 86 608 for a HD patient and 66 751 for a PD patient. Costs for dialysis treatment and directly treatment-related other costs as injectable drugs accounted for 35% of total costs on HD and 37% on PD. Of injectable drugs, costs for erythropoiesis stimulating agencies were the largest (over 6000 on HD and 3600 on PD) and total outpatient medication costs were on average 8482 on HD and 4125 on PD. Cost for hospitalization on HD and PD were 34% and 37% of total costs, respectively. Physicians' costs, which were charged separately, were on average 16 200 on HD and 9900 on PD (Collins et al. 2013). In Germany, cohort of dialysis patients (11% on PD) was studied and costs were measured as health insurance reimbursements. Average total costs were EUR 54 777 in a year, 55% of which were caused by

dialysis therapy. Medication, hospitalization and transportation accounted for 22%, 14% and 8%, respectively (Icks et al. 2010).

Compared with CHD, structure of cost in HHD is different: Because of the increased frequency, the expenses for materials and supplies consumables are higher in HHD. On the other hand, personnel costs are lower. Depending on the development level of a particular country and ratio of cost of personnel to cost of consumables, total cost may be lower or higher in HHD compared with CHD. In developed countries, cost for personnel outweighs cost for consumables favouring HHD (Perl and Chan 2009). In a Canadian study, staffing costs (Canadian \$) were markedly less on HHD compared with CHD (annually 10 932 vs. 22 056) and there was a trend toward lower costs for hospital admissions and for medications whereas costs for HD materials were higher (McFarlane et al. 2002). Decreased rate for hospitalization has been reported (Bergman et al. 2008) but not confirmed (Eknoyan et al. 2002; Chertow et al. 2010; Rocco et al. 2011) in all studies. Lower costs for medication reported to associate with HHD may decrease total costs (Culleton et al. 2007).

In Finnish setting, Malmström et al evaluated costs in HHD and satellite-HD patients. Total annual costs among both modalities were some (EUR) 39 000. 63%–70% of them were caused by dialysis therapy. Medication costs were 13%–18% (EUR 5000–7000) of total expenditures and costs for transportation accumulated on SatHD patients being on the average over 5000 among them. Costs for laboratory, radiology, surgery and hospitalizations in these selected patients accounted for approximately 5–12% of total costs. (Malmström et al. 2008)

In peritoneal dialysis, costs for dialysis fluids and disposables comprise a remarkable proportion of total healthcare costs. In a recent study from Mexico, dialysis related costs accounted for 41% of total expenses in CAPD patients and 47% in APD patients, respectively. Costs for hospitalization were the second largest item, 37% in CAPD and 31% in APD. (Cortes-Sanabria et al. 2013)

2.5.10 Impact of comorbidities on costs

Smith et al. (Smith et al. 1989) compared the charges for ESRD treatment of 244 diabetic patients to 902 non-diabetic patients. In diabetic patients, charges were systematically higher than in non-diabetics: annual charges (US\$) were 27 463 vs. 23 470 on CHD, 29 435 vs. 22 753 on CAPD and 8325 vs. 5696 on CTX (year

after transplant), respectively. Yang and colleagues (Yang et al. 2001) reported 11,8% more expenses in diabetic patients compared to non-diabetics, the difference was mainly caused by higher costs for hospitalization. Study included 106 matched diabetic–non-diabetic pairs. Similarly, in a Canadian study, presence of insulin-dependent diabetes mellitus and ischemic heart disease added 44% and 16%, respectively to costs in multiple regression analysis (Goeree et al. 1995). A British prospective study included dialysis patients aged 70 years and over. Age over 80 years and presence of peripheral vascular disease increased daily treatment costs by over (UK Pounds) 10 compared with patients aged 70–74 years and without peripheral vascular disease. Proximity to death was associated with over 40% increase in daily costs but diabetes was not an independent predictor of costs in this study (Grun et al. 2003).

2.6 Health care organizations and financing of end-stage renal disease programs around the world

Remarkable variety in funding and reimbursements from country to country exist. In public systems (e.g. the Nordic countries, the UK, Canada), health care is financed through taxes to ensure equal access to full range health care services (including RRT programs) to all residents (Prichard 1997; Nicholson and Roderick 2007; Wikstrom et al. 2007). Within countries with mixed public and private providers (e.g. Germany, Spain, France, Italy) there are both free-standing and public facilities providing services for RRT. Regardless of provider, RRT is financed from centralized national health service funds (Jacobs 1997; Piccoli et al. 1997; De Vecchi et al. 1999; Luno 2007; Icks et al. 2010). In the US, a national social insurance program (Medicare) covers over 90% of patients on RRT. Medicare payment to facilities treating ESRD has been based on a system known as the basic case-mix adjusted composite payment system. One composite rate for dialysis treatment and related routine drugs has been paid regardless of modality. This policy is currently being replaced with a bundled ESRD Prospective Payment System and Quality Incentive Program that provides incentives to dialysis facilities to improve the quality of dialysis care (Slinin and Ishani 2013).

In 2012, a survey comparing reimbursement policies in seven countries was published. In addition to the total sums reimbursed for various modalities, the comparison examined composition of the reimbursement package and adjustment in rates for specific patient subgroups in the United States, in the province of

Ontario in Canada and in five European countries (Belgium, France, Germany, the Netherlands and the United Kingdom). Important differences between these countries were found. For CHD, reimbursement per week varied from (US\$) 1668 in the Netherlands to 689 (in the USA) and for CAPD from 1126 (the Netherlands) to 502 (the UK). Except for the United States which provides a fixed amount of reimbursement regardless of modality, home dialysis strategies (HHD, PD) were reimbursed lower than hospital hemodialysis. In the US, costs for intradialytic medications (erythropoiesis stimulating agents, intravenous iron and vitamin D analogues) are included in the amount of reimbursement whereas in Belgium and Germany they are charged separately. The authors acknowledged that even though their survey was limited to seven countries, their approach was sufficient to point out remarkable differences in countries at similar economic level. (Vanholder et al. 2012)

2.7 Macroeconomic factors

Societies' possibilities to provide RRT are strongly dependent on their economic status. Citizens in the less developed countries have very limited possibilities to enter in RRT, whereas e.g. in the USA there is almost universal acceptance for uremia therapy (Friedman 2003). Number of dialysis patients in the USA in 2008 was 1244 per million population compared to 8 per million population in Nigeria (Karopadi et al. 2013). Consequently, it is obvious that patients' characteristics are not equal and comparisons between countries are not straightforward. Incidence of dialysis therapy in a country is associated with the characteristics of the dialysis population and a high incidence of dialysis reflects high acceptance of patients with a poor health condition. Low acceptance in dialysis therapy goes together with younger age, few comorbidities and low mortality risk. In a recent study macroeconomic factors were found to have an effect on international differences in the mortality on dialysis (Kramer et al. 2012). A higher gross domestic product per capita (hazard ratio 1,02 per 1000 US\$ increase) and a higher percentage of gross domestic product spent on healthcare (hazard ratio 1,10 per percent increase) were associated with a higher mortality. Renal service organizational factors seemed less important.

Besides macroeconomic factors, there is relevant divergence in outcomes between dialysis units inside the countries. Several studies have reported unequal mortality between centers (Garg et al. 1999; Devereaux et al. 2002; McClellan et al.

2009; Van Wyck et al. 2010). In the Netherlands, with the publicly funded health care system, significant differences between dialysis centers existed in patients' HRQOL after adjustment for covariates (Mazairac et al. 2012).

2.8 Modality selection

Worldwide, in 2008, of 1,75 million patients on dialysis, 89% were treated by HD while 11% were on PD. In developed countries, the proportion of patients on PD has declined by 5,3% from 1997 to 2008 (Grassmann et al. 2005; van Biesen et al. 2008; Jain et al. 2012). In Finland the average incidence rate of RRT in 2008–2012 was 86 per million population (pmp) and of a total of 1760 patients on chronic dialysis therapy in the end of 2012, 321 (18%) were treated with PD (http://www.musili.fi/files/1280/Munuaistautirekisteri_vuosiraportti_2012.pdf). ERA-EDTA registry includes data on RRT from 30 countries in Europe and bordering the Mediterranean Sea. In overall, the incidence rate of RRT in 2008 among all registries was 122 per million population (pmp) ranging from 264 pmp in Turkey to 15 pmp in Ukraine. The prevalence of HD varied from 66 pmp in Ukraine to 875 pmp in Portugal and the prevalence of PD from 8 pmp in Montenegro to 115 pmp in Denmark. In western European countries the proportion of PD patients of all dialysis patients varied from 5% to 23% (Stel et al. 2011). In the United States 7% of dialysis patients are treated with PD (Collins et al. 2013; Karopadi et al. 2013).

Substantial disparities in access to transplantation exist and TX rates vary markedly across the world, the lowest numbers being in underdeveloped countries. Even in industrialized societies there are significant variations by country after adjusting for differences in case mix. Socioeconomic, cultural and religious nature of a country impact the number of donors and also the patients' view of transplantation. Concept of brain death is not straightforward in different cultures and e.g. in Japan cadaveric TXs are relatively rare despite a well-organized health care system. The highest TX rates in ERA–EDTA region in 2011 were found in Castile and Leon region in Spain (161 pmp) and the lowest in Ukraine (1,4 pmp), respectively. The high TX rate in Spain reflects its active policy in harvesting organs and its higher use of kidneys from older donors. (<http://www.era-edta-reg.org/files/annualreports/pdf/AnnRep2011.pdf>). In the United States, the number of TX were 17 777 in 2010, thus providing TX rate of 57 pmp. 64% of transplants were cadaveric (Collins et al. 2013). In Finland, total number of kidney

transplantations in 2012 was 199 (37 pmp), 11 of which were from living donors. Number of kidney transplant recipients was 2611 (481 pmp), respectively (http://www.musili.fi/files/1280/Munuaistautirekisteri_vuosiraportti_2012.pdf).

Economic factors influencing dialysis mode selection include financing, reimbursement and resource availability (Nissenson et al. 1993; Nissenson 1996; Just et al. 2008). Reimbursement structure has been identified as the most important non-medical factors in modality selection (Nissenson et al. 1993; Nissenson et al. 1997). Generally, PD utilization is low when there is little or no facility reimbursement or physician reimbursement payment for PD (Karopadi et al. 2013) and, in contrast, with equal or higher reimbursement utilization is much higher (Nissenson et al. 1993; Durand and Verger 2006). In public systems with limited HD capacity, efforts are being done to reduce pressure on dialysis centre (Olsen et al. 2010) and patients are directed to PD more often than in private systems which have invested in HD capacity and attempt to exploit the investments maximally (De Vecchi et al. 1999). In certain countries, there is interest to revise the reimbursement policy in a way to encourage utilization of home-based modalities PD and HHD (Nissenson et al. 1997; Mendelssohn et al. 2004; Ghaffari et al. 2013). In Hong Kong approximately 80% of patients are on PD and HD is permitted only if a contraindication to PD exists (Li and Szeto. 2008). In developing countries, market factors play a crucial role in modality selection. The bulk of costs in dialysis arise from the price of dialysis fluids and supplies and HD is economically preferred due to low cost of labour and high cost of imported CAPD bags (Neil et al. 2009; Karopadi et al. 2013).

Absolute medical contraindications for the use of either HD or PD are few. In a prospective evaluation including 1303 predialysis patients at seven North American nephrology practices, 98% of patients were considered medically eligible for HD and 87% for PD, respectively. In this study, contraindications for HD included advanced age, terminal illness, severe heart failure and extensive vascular disease. The major causes of non-eligibility for PD were age and anatomical concerns including hernias, adhesions and overweight. Psychosocially, 83% were eligible for PD and 78% of all patients were assessed as having no contraindications for PD (Mendelssohn et al. 2009). However, the actual proportion of PD is much lower and continues to decline further (Van Biesen et al. 2008; Collins et al. 2013; Karopadi et al. 2013).

Generally, the medical contraindications to PD are related to peritoneal access or peritoneal cavity. Previous major abdominal surgery, large abdominal hernias, severe obesity, active or recurrent diverticulitis and large abdominal aneurysm are

among the most frequent factors which disqualifies the patient from doing PD. Besides contraindications, certain factors are obstacles to PD and make the modality a challenge: impaired vision, insufficient strength, immobility, frailty, poor hygiene, psychiatric illness and impaired memory limit utilization of PD as well as use of any self-care modality (Blake et al. 2013).

Practicing nephrologists in the UK and in the United States have estimated the optimal (i.e. clinical outcomes maximized) ratio of HD to PD at about 60–65:35–40 (Mendelssohn et al. 2001; Jassal et al. 2002). Despite this, actual allocation of PD is much lower. Both medical and particularly non-medical factors contribute to this disparity. There are numerous reasons contributing to the low utilization of PD. In some countries physician and facility reimbursement are related to modality selection, mostly favouring HD. When financial issues are not prominent, utilization of PD is usually higher. This applies for e.g. to the Nordic countries with publicly funded health care systems and salaried physicians (Nissenson et al. 1993). There are also concerns regarding patient survival, modality related infections and small-solute clearance. Lack of experience with PD, physicians' comfort with HD and constituting infrastructure with HD facilities all have contributed to underutilization of PD (Chaudhary et al. 2011). Personal preferences and attitudes influence on decisions and approaches in modality selection change slowly (Blake et al. 2013). The importance of patient education was highlighted in an American study. A majority of patients with advanced chronic kidney disease cared for by nephrologists were unaware of the possibility of PD when perceived knowledge of the therapeutic options for ESRD was assessed (Finkelstein et al. 2008). Patients who are objectively educated about modality options more often choose PD or other self-care dialysis than do uneducated patients (Little et al. 2001; Marron et al. 2005; Neil et al. 2009).

2.9 Modality switch

2.9.1 Epidemiology of modality switch

After having started the treatment, switching of modality is not infrequent. Especially patients on PD commonly experience treatment failures resulting in modality change. In a register based study, less than 80% of 1390 dialysis patients remained on their first type of dialysis after two years (Smith and Wheeler 1987).

Gentil et al reported three-year technique survival (remaining on modality) 94% and 56% on HD and PD, respectively (Gentil et al. 1991). An Italian study found method survival 40% in PD and over 90% in HD, follow-up continued up to nine years (Maiorca et al. 1996) whereas a study from the United States reported 30% treatment failure on PD over 12 months follow-up (Singh et al. 1992). Jaar et al. found that 25% of patients receiving PD and 5% of those on HD switched treatment modality at least once within seven years (Jaar et al. 2005). Shih et al. conducted a register-based survey of over 3400 dialysis patients. Approximately one third of patients who started on PD had one or more modality changes within the first three years compared with less than 1% of the HD group (Shih et al. 2005). In a North American cohort study including 1587 PD patients, 39% had been forced to switch to HD by three years for at least 30 days (Shen et al. 2013).

Changes from one modality to another occur and multiple switches over the course of time are not uncommon. Intention-to-treat and as-treated approaches are applied when patient's modality is classified. When the assignment of modality is done on an intention-to-treat basis, a modality is defined at study start and assignment does not change even if the patient switches to another modality. By intention-to-treat approach, bias resulting from high costs associated with modality switch is avoided. For example, patients who are performed an unsuccessful kidney transplantation and continue dialysis therapy, may have very high costs caused by failure-associated events. If these patients are not regarded as transplant patients and only those with functioning grafts are included in the analysis, costs of transplantation would be underestimated. Contrary, an as-treated approach – defined as modality actually in use at any point in time – would classify these patients according to new modality rather than to the failed modality that brought about the high costs.

2.9.2 Reasons for modality switch

Switching between modalities may occur for a variety of reasons. Potential causes of transfer from PD to HD can be classified as modality related (infections, inadequate dialysis and catheter-related problems), system related (lack of infrastructure or patient education, reimbursement policy) and patient related (comorbid conditions, burnout, social reasons, hernia formation and abdominal surgery) (Chaudhary et al. 2011). Of all causes, modality-related complications are the most common.

The development of PD-devices and supplies has helped to decrease the access-related infection rates (Strippoli et al. 2004) but peritonitis is still the main reason to change from PD to HD, especially within the first two years after initiation of treatment. In Canadian data from 1981 to 1997, the switch rate from PD was estimated to be 154 per 1000 patient-years and trend of a decreasing rate over years were found (Schaubel et al. 2001). A multicenter prospective study evaluated 292 PD patients. Almost 25% of patients experienced a treatment failure, 70% of them within two years of starting PD. Infections (peritonitis and catheter related infections) were the reason for the switch at 37% (Jaar et al. 2009). Peritonitis rates have varied markedly in published studies. In recent literature, an incidence rate ranging between one episode per 12–83 months have been reported (Monteon et al. 1998; Daly et al. 2001; Davenport 2009; Brown et al. 2011; Cnossen et al. 2011; Hsieh et al. 2013; Ortiz et al. 2004; Medani et al. 2012). Insufficient dialysis or management of fluids is not infrequent. The ultrafiltration failure rates from 2% to 14% have been recognized (Jager et al. 1999). Mechanical complications may occur and contribute to switch from PD. Sometimes a patient transfers voluntarily to HD. Overall; trends toward better technique survival in PD over years have been reported (Guo and Mujais 2003).

Reasons for switching from HD to PD include vascular access problems and cardiovascular instability and also patient's own choice. Among HHD patients, lack of confidence in carrying out treatment, interference with home life, family dynamics and fear of self-cannulation may result in modality switch. In the UK, 166 HHD patients were followed for on average 2,3 years. Technique survivals at 1, 2 and 5 years were 98,4, 95,4 and 88,9%. Diabetes and cardiac failure associated with an increased risk of technique failure, but majority of patients switched modality for non-medical reasons (Jayanti et al. 2013).

A cohort study from the United States investigated the determinants of PD technique failure. Over 1500 PD patients were followed for three years. In multivariate analysis, female sex was statistically significantly associated with lower risk of failure whereas risk was increased in blacks, retired and disabled. Interestingly, age, comorbidities, body mass index and educational or marital status did not associate with failure risk (Shen et al. 2013). Contrary, a recent study from Taiwan reported age over 65 to be the only identified risk factor for peritonitis, which subsequently predicted technique failure (Hsieh et al. 2013). In several studies, number of patients in PD centre has positively correlated with better outcomes (Schaubel et al. 2001; Huisman et al. 2002; Afolalu et al. 2009; Plantinga et al. 2009). High number of PD patients in each centre possibly accounts for the

excellent two-year technique survival rate of 82% in Hong Kong (Li and Szeto 2008).

2.9.3 Modality switch and costs

Substantial cost increase may be caused by switches between modalities. Initiation of a new modality is associated with start-up costs which accumulate in repeated switches (Prichard 1997). In a register-based study evaluating Medicare expenditures in dialysis patients over three years, annual costs were significantly lower (23% to 27%) for those patients who were treated on PD as the initial modality. Patients who switched from PD to HD within the first year had higher treatment costs than those who switched later and the economic advantage related to PD was lost among first-year switchers. In those patients who switched to HD for at least 60 days, annual costs increased over (US\$) 20 000 (Shih et al. 2005). In a Canadian study, incident dialysis patients were categorized by initial modality and subsequent modality changes. Total treatment costs during three years were evaluated and a purchaser's perspective was taken. Adjusted cumulative three-year costs (Canadian \$) were 58 724 for patients who received only PD and 175 996 for those who received only HD. Compared with patients on HD-only, costs were similar for patients with a PD technique failure and a change to HD. Costs for patients who changed from HD to PD were in between costs for PD-only and HD-only. The authors concluded that since costs were lower on PD and costs of patients with PD technique failure were not in excess of HD-only patients, the economic rationale for a PD-first policy in eligible patients was supported (Chui et al. 2012).

In HHD, a patient's inability to carry out dialysis procedure leads to technique failure and necessitates a modality change. In a Canadian study utilizing Markov model, annual probability of technique failure in nocturnal HHD was set at 7,6% and HHD dominated CHD. HHD led to incremental cost savings (Canadian \$6700) and an additional 0,38 QALYs. In sensitivity analyses, higher risk of failure markedly increased costs. At an annual failure risk of 19%, CER 75 000/QALY was provided and its attractiveness was lost (Klarenbach et al. 2013). The reported failure rates have been lower in observational studies. In the UK, during an 8-year follow-up including 4528 HHD patient-months, technique failures were uncommon. Technique survivals at 1 and 5 years were 98,4% and 88,9%,

respectively. Age over 60 years, cardiac failure, diabetes and high score in comorbidity index scale were associated with technique failure (Jayanti et al. 2013).

2.10 Hyperparathyroidism

Secondary hyperparathyroidism is a common and almost inevitable metabolic disturbance among patients undergoing maintenance dialysis therapy (Slatopolsky et al. 1999). It develops in response to an imbalance in serum levels of calcium (Ca), phosphorus (P) and vitamin D as a consequence of altered metabolism in chronic kidney disease and it is characterized by increased serum levels of parathyroid hormone (PTH) (Locatelli 2004). Disordered Ca, P and PTH (also known as mineral metabolism markers) concentrations are associated with an increased risk for soft tissue and cardiovascular calcifications. Vascular calcification is a central component in the chronic kidney disease – mineral and bone disorder (CKD-MBD); a complex syndrome which has been indicated to be the basic contributor causing accelerated atherosclerosis, increased cardiovascular morbidity and excess mortality in dialysis patients (Lowrie et al. 1990; Block et al. 1998; Ganesh et al. 2001; Marco et al. 2003; Wang et al. 2003). Higher concentrations of serum Ca and especially P strongly associated with an increased risk of death in a study obtaining data from a database of over 40 000 HD patients (Block et al. 2004) and in another observational study including over 58 000 HD patients (Kalantar-Zadeh et al. 2006). Serum calcium phosphate product (Ca x P) and moderately to severely elevated PTH each correlated with increased mortality risk (Block et al. 1998; Block et al. 2004). Subsequently, central role of P in inducing vascular calcification has been recognized and it has been regarded as a major risk factor for cardiovascular disease in dialysis patients. Over the last years much interest has focused on rigorous control of serum P, Ca and PTH and efforts to reduce serum P levels have become an important priority in practice.

In 2003, the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommended strict targets for the control of serum levels mineral metabolism markers: PTH 16.5–33.0 pmol/l, Ca 2.10–2.37 mmol/l, P 1.13–1.78 mmol/l and Ca x P product <4.4 mmol²/l² (National Kidney Foundation 2003). The guidelines were mostly based on observational studies and made an assumption that correcting biochemical abnormalities would turn to beneficial effects on clinical outcomes. In 2009, new guidelines were given, this time by Kidney Disease:

Improving Global Outcomes (KDIGO). The lack of good quality data about benefits of strict controlling of mineral metabolism markers was acknowledged and the targets in treating Ca, P and PTH in dialysis patients were moderated. Lowering elevated P toward the normal range and maintaining serum Ca in the normal range and PTH at approximately two to nine times the upper normal limit were suggested. Pharmacotherapy to prevent absorption of dietary P were suggested but total amount of elemental calcium provided in P binders was guided not to exceed 1500 mg (KDIGO 2009).

In a remarkable portion of dialysis patients, the levels of mineral metabolism markers lie outside the suggested levels. In The DOPPS; an international observational study including over 17 000 patients from 307 dialysis facilities, overall 51% of dialysis patients were below the K/DOQI suggested low target for PTH whereas the upper level was exceeded in 27% of patients. Ca x P product was above target in 44% of patients and P and Ca in 52% and in 50% of patients, respectively. In this study mortality was also strongly associated with altered mineral metabolism values (Young et al. 2005).

2.10.1 Phosphorus

To lower serum P levels, P binders are utilized to prevent the absorption of dietary P from the intestine. Calcium salts have been the most widely prescribed P binders in dialysis patients (Qunibi and Nolan 2004). They are effective in lowering P levels but, when taken in large amounts and particularly in combination with vitamin D, there is concern about their association with hypercalcaemia and accelerated vascular calcification (Goodman et al. 2004; Hutchison 2009).

Despite strong connection between mortality and elevated serum P in observational studies, there is a lack of data that a pharmacological reduction of P will turn to improved survival among dialysis patients (Bushinsky 2006). Also the central role of P in causing vascular disease has been questioned. Post hoc analysis of data collected in Modification of Diet in Renal Disease (MDRD) did not confirm the association between elevated serum P and mortality (Menon et al. 2005). Recently, higher serum P was found in individuals with CKD and lower socioeconomic status, which is an important and an independent risk factor of mortality and morbidity (Gutierrez et al. 2010). Even though phosphate restriction has been found to reduce mortality in uremic rats (Finch et al. 2013) and parathyroidectomy, by relieving hyperparathyroidism and reducing Ca, P and Ca x

P product towards normal levels, may decrease morbidity and mortality in severe cases (Sharma et al. 2012; Goldenstein et al. 2013), there is no clear evidence on clinical benefits of the use of P binders. However, results favouring the use of P binders were found in a recent multicenter open-cohort observational study (COSMOS study, 6797 patients) which evaluated outcomes among P binders prescribed European HD patients compared with those who were not on P binder therapy. After multivariate analysis, 29% lower all-cause and 22% lower cardiovascular mortality were reported in P binder prescribed patients. The authors stated that the observational nature of study provides associations but precludes from making conclusions on causality and they emphasized the need of a clinical controlled trial to test the effects of P binders (Cannata-Andia et al. 2013).

Due to the concern over the possible risks caused by calcium loading, considerably more expensive non-calcium based P binders sevelamer hydrochloride and lanthanum carbonate have been introduced. Like calcium salts, these compounds are utilized to prevent P absorption from the intestine. Theoretically, non-calcium-based binders have an advantage over calcium-based binders by not inducing hypercalcaemia. Nevertheless, no significant differences in overall mortality between different P binders have been found in randomized clinical studies like The Dialysis Clinical Outcomes Revisited (DCOR) trial (St Peter et al. 2008) or two other studies (Suki 2008; Wilson et al. 2009). Survival advantages associated with lanthanum and sevelamer over Ca-based P binders in the subgroups of patients over 65 years were reported by Wilson et al. and Suki et al., respectively (Suki et al. 2007; Wilson et al. 2009). In a small randomized trial including 127 patients new to hemodialysis, treatment with sevelamer was associated with survival benefit compared with Ca containing P binders (Block et al. 2007). On the other hand, in a French observational study calcium-based P binders were associated with lower mortality compared with sevelamer (Jean et al. 2011). A review (Tonelli et al. 2010) and two meta-analyses (Jamal et al. 2009; Navaneethan et al. 2009) stated that there are no apparent advantages favouring of one kind of P binder over other.

2.10.2 Parathyroid hormone

Association of PTH with mortality has been found to show a U-shaped curve, with an increased risk of death at both high and low concentrations (Block et al. 2004; Tentori et al. 2008; Floege et al. 2011) and there has not been consistency regarding

the optimal level of PTH. For that reason, the KDIGO guidelines could only suggest targeting PTH levels into moderately elevated range and avoiding extreme increases. Treatment options for elevated PTH caused by hyperparathyroidism include active vitamin D, the calcimimetic cinacalcet, phosphate binders and surgery (Vervloet et al. 2013).

The calcimimetic agent cinacalcet hydrochloride inhibits the release of PTH by increasing the sensitivity of the calcium sensing receptor to extracellular calcium thus reducing circulating level of PTH (Nemeth et al. 1998). The cost of cinacalcet is relatively high when compared with calcium-based P binders. Soon after its approval, reduction in the rate of cardiovascular events and in the rate of parathyroidectomy was reported (Cunningham et al. 2005). Nevertheless, when the impact of cinacalcet on mortality was studied in EVOLVE study, a randomised controlled trial including 3883 HD patients with median duration of 21 months, no significant difference between the groups was shown (Chertow et al. 2012). The high dropout rate and the number of patients who were prescribed cinacalcet as a part of their regular therapy possibly hampered the study.

2.10.3 Vitamin D

Disordered vitamin D metabolism is a major contributor in the development of CKD-MBD (Moe et al. 2006). In cross-sectional studies, vitamin D deficiency has been found to associate with increased mortality in general population (Skaaby et al. 2012; Zittermann et al. 2012) and vitamin D supplements in combination with calcium have been found to reduce mortality among elderly individuals (Rejnmark et al. 2012). In a German cohort including over 6500 HD patients, 41% were severely vitamin D deficient and, compared with those with normal vitamin D levels, their risk of death was more than doubled (Krause et al.). In another study from Germany, risks for sudden cardiac death and all-cause mortality were found to three-fold and 1,74-fold, respectively, in vitamin D deficient HD patients compared with non-deficient (Drechsler et al. 2010).

Several studies have evaluated benefits of vitamin D supplementation among dialysis patients. In a historical cohort including over 51 000 patients, injectable vitamin D provided a survival advantage of 26% compared with patients who did not receive vitamin D. The benefit was evident in 48 of 49 strata and subgroups tested, including those with elevated levels of serum Ca and P, situations in which vitamin D is usually avoided (Teng et al. 2005). Another large observational study

with over 58 000 patients on HD found improved survival associated with any dose of injectable paricalcitol over those who were not on vitamin D treatment (Kalantar-Zadeh et al. 2006). Shinaberger et al. studied the ratio of administered paricalcitol to patient's PTH and a dosage-response association between survival and PTH-adjusted dose of vitamin D was found (Shinaberger et al. 2008). To explore differences between vitamin D products, outcomes in patients receiving calcitriol, paricalcitol or doxercalciferol were compared with each other and with those who were not prescribed vitamin D. After adjustments for covariates, no differences between the three compounds were found and survival benefit was present when compared to those who did not receive vitamin D (Tentori et al. 2006). Wolf et al reported a higher proportion of black patients on HD receiving vitamin D compared to white patients and speculated that the higher utilization of vitamin D possibly explained the improved survival among blacks (Wolf et al. 2008). Conclusion in the systematic review deriving from Cochrane Database was that there are observational data supporting the possible decreased mortality associated with vitamin D compounds, but power of studies so far is inadequate to confirm their effect on clinically relevant outcomes (Palmer et al. 2009). In a recent meta-analysis, outcomes of vitamin D therapy in CKD were assessed. Twenty observational studies were included in the analysis, 17 of them reported dialysis patients. Results were clear: vitamin D compounds were significantly associated with a reduced risk of mortality both among dialysis patients and CKD patients not requiring dialysis therapy. Naturally, the need for large randomized trials was acknowledged (Zheng et al. 2013).

2.10.4 Mineral metabolism disorders and costs

Not much is known about the association between levels of serum mineral metabolism markers and treatment costs or HRQOL in dialysis patients. In a large retrospective cohort study, relationship between mineral metabolism markers and hospitalizations and costs among European hemodialysis patients were examined. Altogether 6369 patient were included in the analysis. Patients with elevated PTH (over 66 pmol/l) had a higher hospitalization rate compared with those with lower PTH and, after adjustment of covariates, their total healthcare costs were 41% higher than costs in patients with PTH in the K/DOQI target. Ca and P levels had minor impact on hospitalization rates but adjusted costs were 25% lower in

patients with P below the target range (1,13 mol/l) compared with those with higher level. Ca level did not significantly associate with costs. (Chirolì et al. 2012)

No prospective studies so far have shown a clear benefit of the use of P binders or differences favouring one P binder over another (Bushinsky 2006; Tonelli et al. 2010). Nevertheless, in the DCOR study, a beneficial effect on all-cause hospitalizations and hospital days associated with sevelamer compared with Ca-based P binders was found. However, after costs from P binders were incorporated, this economic advantage was lost and overall expenses were lower on patients on Ca-based treatment (St Peter et al. 2009). Earlier, a 50% reduction in hospitalization rate and almost (US\$) 1400 lower monthly Medicare expenditures in sevelamer prescribed patients compared with patients not on sevelamer have been found in a case-controlled study (Collins et al. 2000). A study using a life-long Markov model reported second-line lanthanum carbonate therapy in dialysis patients to be cost-effective at ICER (UK Pounds) 6900 per QALY gained (Vegter et al. 2011). Similar results were given in Japan: An open-label trial examined lanthanum carbonate as a second-line treatment and, based on those results, a transition model were developed. Additional lifetime costs exceeded (US\$) 22 000 and 0,632 QALYs were gained, thus providing an ICER almost 35 000 per QALY (Goto et al. 2011).

To establish the effectiveness and cost-effectiveness of cinacalcet in secondary hyperparathyroidism for dialysis patients compared with standard treatment, several studies have utilized a Markov model incorporating data derived from clinical trials. Garside et al. modelled 40% and 5% of patients in cinacalcet treatment and standard treatment, respectively, to meet target level (K/DOQI guidelines) in PTH. Significant reduction in rates of fractures and parathyroidectomies were determined in cinacalcet patients, all-cause mortality was set equal. By using these assumptions, compared to standard treatment, additional costs (UK Pounds) in cinacalcet treatment were over 21 000 and 0,34 QALYs were achieved. ICER was 61 890 per QALY thus exceeding the 30 000 Pounds willingness-to-pay threshold (Garside et al. 2007). Similarly, in an Italian model ICER (EUR) 67 361 were reported in cinacalcet treated patients compared to standard therapy (Eandi et al. 2010). Results of the EVOLVE study, the largest prospective randomized study evaluating effect of cinacalcet in dialysis patients to date, support these findings. The EVOLVE study did not focus on economic aspects, but as treatment with cinacalcet neither provided any survival advantage nor reduced cardiovascular events, its cost-effectiveness is not probable (Chertow et al. 2012). In another model, cinacalcet treatment was not compared with

standard therapy but the setting was early versus late cinacalcet treatment added to standard therapy. ICER (US\$) 17 275 in the early use of cinacalcet was reported (Ray et al. 2008).

Association of PTH and HRQOL was evaluated in a case-control study from Greece. HRQOL was compared between patients with low serum PTH (<300 pg/ml) and high PTH (>300 pg/ml). After adjustment of covariates, higher PTH level was associated with worse pain and lower physical component summary and patients with low PTH scored better in 18 out of 23 domains (Malindretos et al. 2012).

In a prospective cohort study in the United States, patients with vitamin D deficiency experienced higher hospitalization and mortality rates compared with those with higher serum levels (Anand et al. 2013). In a German prospective study with 81 patients on HD, low vitamin D concentration associated with poorer survival but not with hospitalization over a three-year follow-up (Fiedler et al. 2011). In PD patients, treatment with vitamin D was independently associated with lower risk of peritonitis in two retrospective studies (Rudnicki et al. 2010; Kerschbaum et al. 2013).

When comparing economic effects of different vitamin D compounds, intravenous paricalcitol decreased hospitalization costs more effectively than calcitriol or alfacalcidol (Rosery et al. 2006). Similar results were given in another study, which compared paricalcitol with calcitriol. Paricalcitol-treated dialysis patients had 14% lower risk of all-cause hospitalization and 6,8 fewer hospital days in a year. The authors stated that initiating vitamin D therapy with paricalcitol may result in over (US\$) 7600 annual savings (Dobrez et al. 2004).

An additional connection between treatment of hyperparathyroidism and HRQOL was found when the impact of daily medication was evaluated. A remarkable amount of different compounds are needed to effectively treat mineral metabolism disorders in dialysis patients. Due to other co-existing diseases and symptoms, the daily pill burden in these patients is high. In a prospective observational study, the median number of daily pills was 19 and in one-quarter of patients the number exceeded 25. P binders accounted for one-half of pill burden. Only 38% of patient were adherent to P binder therapy (determined as consuming at least 80% of prescribed pills). High total number of pills was found to independently associate with low scores on the physical dimensions of HRQOL (Chiu et al. 2009).

2.11 Malnutrition and inflammation

Malnutrition and chronic inflammation are common and often concomitantly occurring disturbances in dialysis patients (De Mutsert et al. 2008). Due to the association with atherosclerotic cardiovascular disease, the combination of the two has been referred to as 'malnutrition-inflammation complex syndrome' (MICS) (Kalantar-Zadeh et al. 2003) or 'malnutrition inflammation atherosclerosis' (Stenvinkel et al. 2000). Uremic malnutrition (Pupim et al. 2004), uremic cachexia (Mak et al. 2006) and protein-energy malnutrition (Lindholm et al. 2002) are other terms which have been used to describe conditions associated with loss of muscle and fat tissue and inflammation in CKD patients. Thereafter, protein wasting caused by an increase in protein catabolism, rather than malnutrition in itself, was found to be the major contributor in the complex and it was also found to predict cardiovascular mortality in dialysis patients (Beddhu et al. 2004; Stenvinkel et al. 2004). The need for a uniform and exact nomenclature and definition was recognized and the term 'protein-energy wasting' (PEW) was suggested by an expert panel to incorporate different aspects related to malnutrition, inflammation and other metabolic and nutritional derangements (Fouque et al. 2008; Kovesdy et al. 2009).

PEW is defined as a state of decreased body stores of protein and energy fuels and it is frequently associated with a diminished functional capacity (Fouque et al. 2008). For the diagnosis of PEW, the expert panel has recommended four categories be recognized: 1) biochemical criteria including low serum levels of albumin, prealbumin or cholesterol; 2) low body weight or weight loss or reduced total body fat; 3) reduced muscle mass and 4) unintentionally low dietary protein or energy intake (Fouque et al. 2008). Other potential tools which may be utilized for the diagnosis of PEW include appetite assessment questionnaires, body mass and composition measures and serum levels of transferrin, inflammatory markers and blood lymphocyte count (Fouque et al. 2008).

Therapeutic options to treat PEW include optimizing dietary intake, correcting metabolic acidosis and hormonal disturbances, ameliorating chronic inflammation and prescribing sufficient dialysis. Effectively administered nutritional supplementation to replenish energy and protein stores, physical exercise, appetite stimulants and medical treatment including anabolic steroids and newer anabolic agents may be applied. In observational studies improvement in surrogate markers of nutrition has associated with improved survival, but no randomized clinical trials

have tested its effectiveness in decreasing mortality or morbidity (Ikizler et al. 2013).

2.11.1 Etiology and epidemiology of malnutrition and inflammation in patients on dialysis therapies

Decreased stores result from the imbalance between protein degradation and synthesis which may simply be caused by an inadequate intake. This was demonstrated in a Chinese study which enrolled 305 PD patients and a follow-up continued for 44 months. Patients with protein intake over 0,94 g/kg/day (the highest third) had significantly higher serum albumin and lower risk of death compared to patients in the lowest third with protein intake below 0,73 g/kg/day (Dong et al. 2011).

Besides insufficient nutrition, there are other important conditions resulting in protein depletion in dialysis patients. Mechanisms causing loss of muscles and adipose tissue are complex. The regenerative potential in skeletal muscles is specifically impaired in uremia (Bonanni et al. 2011) and several uremia-related conditions further intensify catabolism. These include systemic inflammatory response (Stenvinkel et al. 1999), acidemia (Chiu et al. 2009), recurrent infections (Dalrymple and Go 2008), nutrient and blood losses during dialysis, dietary restrictions and loss of appetite, endocrine disturbances (Kalantar-Zadeh et al. 2003) and oxidative stress (Nguyen-Khoa et al. 2001).

Precise mechanisms that activate an inflammatory cascade in these patients and induce atherosclerosis are unknown but there is overlap among possible etiologic factors for protein wasting and inflammation (Kalantar-Zadeh et al. 2003). Due to low levels of antioxidants (e.g. vitamins C and E) and subsequent deficiency in their antioxidant system, CKD patients are prone to oxidative stress, which damages tissues and causes inflammation (Nguyen-Khoa et al. 2001). On hemodialysis, exposure of blood to bioincompatible membranes and impurities in dialysis water may activate inflammatory processes (Schiffl et al. 2001). Constant exposure to peritoneal catheter and dialysis solutions may induce inflammation (Kalantar-Zadeh et al. 2003). Inflammation can be assessed by measuring serum level of inflammatory biomarkers as a surrogate. Of these markers, C-reactive protein (CRP) is the single most used. Serum levels of CRP and pro-inflammatory cytokines increase as glomerular filtration rate declines and clearance decreases (Panichi et al. 2002; Eustace et al. 2004).

In European dialysis patients protein-energy malnutrition and chronic inflammation are common. In a Dutch study, 29% of patients entering in HD were malnourished (Jansen et al. 2001) and an observational study from Spain reported 40% prevalence of PEW in single center HD patients (Gracia-Iguacel et al. 2013). In a cohort study including 815 HD patients, 11% suffered from chronic inflammation (defined as serum CRP level over 10 mg/l) (De Mutsert et al. 2008). A South Korean study with 213 PD patients reported 14% having both PEW and cardiovascular disease and 27% had PEW without diagnosed cardiovascular disease. Both PEW and cardiovascular disease were more prevalent in diabetics compared to non-diabetics (Chung et al. 2010). In a prospective study from the United States, the median serum CRP level in 91 patients was 5,3 mg/l (Yeun et al. 2000) whereas the median CRP level in general population has been found to be 1,7 mg/l, respectively (Marott et al. 2010).

2.11.2 Evaluation of malnutrition and inflammation

Scoring systems have been developed to evaluate the nutritional status of dialysis patients. Of them, the Subjective Global Assessment of nutritional status (SGA) is widely utilized. In the SGA, the patients' weight change, dietary intake, loss of subcutaneous fat and signs of muscle wasting are scored to represent the overall nutritional status (Detsky et al. 1987; McCusker et al. 1996). The SGA has been concluded to be reliable and valid for assessing PEW (Steiber et al. 2007) and it was recommended for assessing the nutritional status of dialysis patients by K/DOQI in 2000 (National Kidney Foundation 2000). However, in 2007 European Best Practice Guidelines (EBPG) questioned its validity by claiming that the SGA can only be used to detect severe malnutrition (Fouque et al. 2007). Nutritional risk screening (NRS 2002) is another tool which can be used to identify patients who may benefit from nutritional support (Kondrup et al. 2003).

In 2001, the Malnutrition–Inflammation Score (MIS) was introduced. In MIS, components of SGA are combined with body mass index, serum albumin level and total iron-binding capacity to represent serum transferrin level. During 12 months follow-up, MIS was superior to its components in predicting mortality and hospitalizations in HD patients (Kalantar-Zadeh et al. 2001). Thereafter, MIS has been reported to correlate with clinical and nutritional outcomes in PD patients (Afsar et al. 2006; He et al. 2013) and to associate with endothelial dysfunction in HD patients (Demir et al. 2010). MIS requires subjective assessment by the

examiner and nutritional evaluation of patients with certain conditions may be difficult (e.g. mental disabilities or acute gastrointestinal pathology independent of nutritional factors). To override this problem, the Objective Score of Nutrition on Dialysis was developed. The score is based on objectively measurable criteria and in an observational cohort study it was found to correlate significantly with MIS, hospitalization days and frequency of hospitalization (Beberashvili et al. 2010).

A German study compared individual methods to diagnose malnutrition in HD patients. 90 patients were included in the study and a follow-up continued up to three years. Scores based on clinical evaluation (body mass index, SGA, MIS and NRS 2002) were compared with biochemical laboratory parameters measuring CRP, protein and lipid metabolism and bioelectrical impedance analysis which quantifies body composition. After adjustments for covariates, the best predictive values for mortality were given by the clinical nutrition scores. Of them, MIS >10 provided hazard ratio 6,25. Serum levels of albumin, prealbumin and transferrin associated inversely with mortality and hospitalization and level of CRP correlated directly with hospitalization, respectively (Fiedler et al. 2009). In the Netherlands, a prospective observational multicenter study applied SGA to assess nutritional status in 1601 dialysis patients. 23% and 5% of them had moderate and severe PEW, respectively. PEW at baseline was associated with a death risk of 2-fold of that of patients without PEW. The authors concluded – contrary to EBPG – that SGA may be a valid tool to distinguish clinically relevant different stages of PEW (De Mutsert et al. 2009).

Low hand grip strength was found to independently associate with higher scores in tests measuring malnutrition and inflammation in HD patients in a cross-sectional study. The association remained after adjustment for confounding factors and the authors suggest that this simple test may be a valid screening instrument for PEW (Silva et al. 2011).

2.11.3 Effect of malnutrition and inflammation on outcomes in patients on dialysis therapies

Several mechanisms may activate PEW and chronic inflammation, which, in turn, were shown to be closely linked to endothelial dysfunction. In a South Korean study endothelial function of 105 PD patients and 32 healthy controls were assessed by measuring flow-mediated vasodilatation. Serum CRP level independently associated with endothelial dysfunction and those PD patients who

had a good nutritional status and no inflammation also had a well preserved endothelial function (Choi et al. 2010).

PEW and chronic inflammation have been reported to associate with a poor outcome in dialysis patients and combination of the two further increases risk. In a Japanese prospective study, 1228 HD patients were followed up to ten years. In patients, who at the initiation of HD were in the lowest quartiles for serum albumin, body mass index and in the highest quartile of serum CRP, adjusted hazard rates for all-cause mortality were 1,97, 2,61 and 3,13, respectively. Hazard rate 8,07 was given with the combination of all the three factors (Takahashi et al. 2012). Similar results were reported in South Korean PD patients. In a prospective study, both PEW and low serum albumin concentration were independent risk factor for mortality. Especially in diabetics, coexistence of both PEW and cardiovascular disease induced death risk that was 3,3 times that of diabetics without them (Chung et al. 2010). MIS was an independent indicator of cardiovascular and infective events in PD patients and it predicted outcomes with the same strength as did Charlson Comorbidity Index, a scale that has been developed for general medical patients (Charlson et al. 1987; Ho et al. 2010). In a study with 560 HD patients, plain serum albumin predicted risk of death with similar strength as did a more complex score generated by multiple parameters (Mazairac et al. 2011). Contrary to these results, survival of HD patients suffering from PEW did not differ from that of patients without PEW during almost three year follow-up in a small Spanish observational study (Gracia-Iguacel et al. 2013).

In the United States, observational data indicate better survival in African American and Hispanic HD patients compared with non-Hispanic white patients, even though in general population mortality among African Americans exceeds that of whites (Collins et al. 2013). In a large cohort study including over 124 000 HD patients, after adjustments of surrogates of malnutrition and inflammation, this advantage in survival was lost and the authors stated that nutritional and inflammatory status may explain differences in mortality between various ethnic populations (Streja et al. 2011).

Associations linking PEW with mineral metabolism have been found. Vitamin D deficiency with concomitant PEW was an independent predictor of mortality in a study which evaluated outcomes in 81 HD patients over a three-year follow-up. Compared with patients without PEW and vitamin D deficiency, hazard rate 5,88 for death was reported (Fiedler et al. 2011). In another prospective multicenter study including over 700 non-diabetic HD patients, dialysis fluid calcium concentration and PEW were evaluated. High-calcium dialysate was associated

with elevated levels of inflammatory markers and lower level of serum albumin than standard-calcium and low-calcium dialysate. The dialysate calcium concentration also independently predicted mortality: hazard rate of death of the patients in the high-calcium group was 2,8 times that of the patients in the low- and standard-calcium groups. (Hsu et al. 2010)

Few studies have evaluated associations between costs or HRQOL and nutritional status or inflammation. Goeree et al found that, after controlling for confounding factors, each 1 g/l decrease in serum albumin was associated with a 4% increase in treatment costs whereas age, sex, diabetes or heart disease had no effect on costs (Goeree et al. 1995). In an American prospective study including over 700 HD patients, lower HRQOL scores correlated with PEW markers (low serum levels of albumin and creatinine) and also with obesity but no association between inflammation and HRQOL was found. Low self-reported mental and physical HRQOL strongly associated with a risk of death and especially a score for mental health was a powerful predictor of survival (Feroze et al. 2011). Similarly, during 5 years of follow-up of 809 HD patients, those with higher MIS had lower HRQOL and high scores also associated with poorer survival rates (Rambod et al. 2009).

2.12 Peritoneal dialysis catheter insertion

The presence of a well-functioning peritoneal dialysis catheter is necessitated in PD. Different protocols for peritoneal dialysis catheter insertion (PDCI) exist but there is no consensus about the preferred operative technique (Hagen et al. 2013). Conventionally, patients have been admitted for the procedure. Catheter-related complications, such as infections, leakage, obstruction and migration cause hospitalization and may lead to treatment failure and modality switch. These problems have been reported as a cause up to 20% of patients changing from PD to HD (Flanigan and Gokal 2005). Hospitalization and treatment failures substantially contribute to treatment costs. In PD, inpatient costs – together with costs for medication – have been found the most important cost-producing item after direct dialysis-related costs. Of total costs, the proportion of hospitalization costs has varied in between 12%–40% (Bruns et al. 1998; Grun et al. 2003; Collins et al. 2013; Cortes-Sanabria et al. 2013). A Canadian study reported a median hospitalization in 106 cases of 4,5 days for an open surgical PDCI (Agulnik and Hirsch. 2001). Avoiding unnecessary admissions may result in savings.

Of the insertion techniques, open surgical method is the most commonly utilized. Other options for the insertion include laparoscopic and radiological techniques. Catheters can also be placed percutaneously without visual control with a trocar or with a Seldinger technique (Brunier et al. 2010). In a British study, 45 PD patients were randomized to either surgical or laparoscopic catheter placement. Compared with open surgery, laparoscopic technique was slower but no differences in outcomes were found (Wright et al. 1999). Another randomized trial from Greece included 50 patients. In 25 patients with open surgical PDCI, operative time was seven minutes less than in laparoscopic patients but leakage and migration occurred statistically significantly more. According to the authors, compared with open surgery, laparoscopic PDCI leads to a better catheter function allowing immediate start of dialysis (Tsimoyiannis et al. 2000). Crabtree et al. reported results in a prospective cohort study including 150 laparoscopic and 63 open surgical PDCIs. Better catheter survival and lower complication rate were found in patients with laparoscopic PDCI (Crabtree et al. 2000). Results favouring laparoscopic PDCIs have also been found in retrospective cohort studies (Gajjar et al. 2007; Lund and Jonler 2007). In Taiwan, Jwo et al. reported contrary results. They conducted a randomized trial with altogether 77 PD patients. A longer operation time and higher costs were found in laparoscopic patients and no difference in catheter survival was found. The authors concluded that since the laparoscopic PDCI seemed to be less cost-effective, the conventional open surgery PDCI is recommended for most patients (Jwo et al. 2010). Recently a meta-analysis comparing laparoscopic and open surgery PDCI was published. Three randomized studies and eight cohort studies were included in the analysis. Of nine postoperative outcomes measured, seven were not different but the proportion of catheter migration was lower and one-year catheter survival was higher in the laparoscopic group (Hagen et al. 2013).

In the last years, a procedure of radiological PDCI under fluoroscopic control has been introduced. Compared with surgical procedure, radiological placement requires less personnel and time. A Canadian single-centre study reported results from a historical cohort of patients that had their first PD catheter implanted. Over a seven-year period, 88 catheters were placed by interventional radiology and 125 catheters by surgical insertion. Radiological PDCI was associated with a high rate of outpatient placement; 70% were placed by same-day-procedure compared with 32% in surgical PDCI. No excess of complications were found (Brunier et al. 2010). Voss et al. reported results from a study comparing radiological PDCI under local anaesthesia with laparoscopic PDCI under general anaesthesia. This

randomized study from New Zealand included 113 patients and the primary endpoint was the complication-free survival by day 365. In the radiological group, 42,5% of catheters survived for one year without complications compared with only 18,1% of laparoscopically inserted catheters. No significant difference in patient survival between the groups was found but costs for hospitalization were significantly higher in the laparoscopic group. The authors concluded that the radiological PDCI is a clinically non-inferior and cost-effective alternative to surgical laparoscopic insertion. (Voss et al. 2012)

A recent Korean study compared a trocar-based percutaneous implantation with open surgical technique. 167 patients were included in the study and percutaneous technique was applied in 89 cases. No difference in overall complication rate was found but the incidence of early mechanical complications (within 15 days) was 11,2% in the percutaneous group compared with 0 in the open surgery group. Rates of catheter removals due to early mechanical complications were 7,9% and 1,3% in the percutaneous and open surgery groups, respectively. Total three-month catheter-related complication rates were 44,9% and 30,8% (Park et al. 2014). In another study comparing percutaneous technique with surgical insertion in 121 pre-dialysis patients, no differences in complication rate or survival were found (Chula et al. 2013). An Irish comparative analysis including 313 PDCIs found more exit-site leaks but better three-month catheter survival in percutaneous patients compared with surgical patients (Medani et al. 2012).

Few studies have directly compared outpatient PDCI with an inpatient procedure. In 2002 Verrelli et al reported their single-centre experience in Canada. During a three-month follow-up, 90 PDCIs out of total 196 were placed on an outpatient basis. No significant difference in complication rates between the groups was found. 6,7% of outpatient patients returned to hospital within 24 hours of discharge, mostly for bleeding. All episodes were self-limited and admissions were not needed (Verrelli et al. 2002). In the same year, Chang et al described results from a ten-year follow-up at a single institution. Their study included 225 patients and 251 PDCIs, 165 of which were outpatient. There were 18 catheter-related complications during the first seven days, most of them were minor and catheter survival at one year was 84% (Chang et al. 2002). Authors of the two reports concluded that outpatient PDCI is safe and hospitalization is not necessary.

In the literature, catheter failure rates vary across the centres. Recently, Chinese and Korean studies have reported the first year probability of catheter survival as high as over 96% (Ouyang et al. 2014) and 93% (Park et al. 2014). A cohort study with 1587 nationally representative PD patients from the US described the actuarial

technique one-year survival of 80,2% and the median survival was 2,7 years (Shen et al. 2013). In an Irish study technical catheter survival by 12 months was found 77,7% in percutaneous PDCI patients and 68,7% in open surgery patients and overall rate of drainage failure was 10,2% in a year (Medani et al. 2012). In a cohort study from the US with 315 patients who had their first PDCI, 92,9% of catheters had not been lost by one year (Singh et al. 2010). Lower rates have been reported in previous studies from the 1990s. In a prospective survey with 72 patients who had a surgical PDCI, the one-year catheter survival was 62,5% (Gadallah et al. 1999) and in another study including 203 PD-patients, 75% of catheters were functioning over one year (Apostolidis et al. 1998). Ortiz et al demonstrated that only 3% of catheters had been lost by 2 years in a prospective study. 125 PDCIs were included in their study and the average follow-up was almost two years. A total of 59 complications were observed, most of them were minor (Ortiz et al. 2004). Nodaira et al. examined risk factors and causes which contributed to removal of PD catheter. In 473 patients the average duration of PD was 5,6 years. The PD catheter was removed from 63 patients, in 47% because of peritoneal infection and in 17% due to dialysis failure (Nodaira et al. 2008). However, as the effect of 579 peritonitis episodes on PD catheters were studied, only 12% of the episodes led to catheter removal (Yang et al. 2008).

3 AIMS OF THE STUDY

The purposes of the present study were:

1. To evaluate costs and distribution of costs in patients treated with various RRTs
2. To evaluate and compare cost-effectiveness between hemodialysis and peritoneal dialysis
3. To find associations between dialysis patients' treatment costs and serum levels of mineral metabolism markers, CRP and albumin
4. To compare outcomes and costs between inpatient and outpatient PDCIs

4 SUBJECTS AND METHODS

4.1 Subjects

Description of the patient groups in Studies I–IV is shown in Table 7.

4.1.1 Studies I and II

Studies I and II focused on costs and cost-effectiveness of RRTs. These studies comprised all the adult ESRD patients who started their RRT for the first time between January 1, 1991 and December 31, 1996 at Tampere University Hospital (TaUH). The follow-up started on the day dialysis therapy was first performed and continued until the end of 1996, death, loss to follow-up or renal function recovery. Total 214 patients (120 males and 94 females) entered dialysis therapy during the study period. Their files were studied retrospectively and the use of services and resources that give rise to costs was identified. The mean age of all patients was 57 years (51 years in those starting on PD and 59 years in HD, respectively). The cause of the ESRD was obtained from patients' files. In 86 (40%) patients ESRD was caused by primary renal disease (chronic glomerulonephritis, interstitial nephritis or polycystic kidney disease) and in 76 (36%) patients the underlying cause was diabetic nephropathy. Of all patients, altogether 55 (26%) patients received a CTX during the follow-up.

4.1.2 Study III

In Study III, association between costs and levels of serum mineral metabolism markers (Ca, P, PTH), albumin and CRP were evaluated in dialysis patients. Subjects in Study III were a subgroup of patients in studies I and II. Of altogether 214 patients who started dialysis therapy during the study period, 111 remained in dialysis at least one year. Of them, two cases with no available laboratory results were excluded. Thus, total 109 patients (62 males and 47 females) were included in

the analysis. Mean age of the patients was 57 years, 68 of the patients started on HD and the average follow-up lasted for 28 months.

4.1.3 Study IV

In Study IV, costs and short term outcomes (within 90 days) were compared between inpatient and outpatient PDCI. Subjects in Study IV were adult patients who were inserted a peritoneal dialysis catheter at TaUH between 1 January 2004 and 31 December 2009. All PDCIs during the period were included in the study. Data were collected from the patients' electronic files. Altogether 106 catheters were inserted during the follow-up. Mean age of the patients was 55 years and 65 of them were males. In 46 cases patients were electively admitted for PDCI and in 19 cases catheter insertion took place during admission for other medical reason or the need to acutely start RRT. Forty-one catheters were inserted on an outpatient basis.

Table 7. Description of the patient groups in Studies I–IV

	Description of study population	Number of subjects	Sex, number (F/M)	Age, years, mean (range)	Follow-up, months, mean (range)	Start on HD/PD, number	Primary renal disease as a cause of CKD, number (%)	Diabetic nephropathy as a cause of CKD, number, (%)	Transplanted, number (%)	Death, number (%)
Studies I and II	All adult ESRD patients entering RRT in 1991–1996 at TaUH	214	94/120	57 (15–84)	25 (0,2–70)	138/76	86 (40%)	76 (36%)	55 (26%)	72 (34%)
Study III	Subgroup of patients in Studies I and II. Duration of dialysis at least one year	109	47/62	57 (16–80)	28 (12–67)	68/41	45 (41%)	40 (37%)	27 (25%)	35 (32%)
Study IV	A peritoneal dialysis catheter insertion in 2004–2009 at TaUH	106	41/65	55 (20–91)	17 (0–52)	–/106	37 (35%)	48 (45%)	36 (34%)	18 (17%)

4.2 Methods

4.2.1 Modality definition

In Studies I, II and III modality was defined on an intention-to-treat basis. HD group consisted of patients starting on HD and those starting on PD belonged to PD group. Subjects who acutely were obliged to start with HD but changed to PD within 30 days were regarded as PD patients. Transplant recipients in Studies I and II were considered as having started a new life-track and they were examined as a new modality group. Study IV included solely PD patients, all the subjects were planned to start their RRT on PD.

4.2.2 Costing procedures in Studies I, II and III

When assessing costs, the perspective of service providers was taken. In Studies I, II and III total direct health care costs arising from the use of health care services were taken into account and overhead costs due to infrastructure, administration and amortization were included. Costs for transport were taken into account. Costs for loss of productivity were not evaluated. In Studies I to III all resource use was valued at the prices in 1997 and costs were converted to United States dollars using an exchange rate of US\$1 = 5.1944 Finnish Marks = 0.8736 EUR.

The number of HD sessions and the amount of consumed PD fluids and equipment during the follow-up were recorded. The cost for a single HD treatment was (US\$) 193 and the daily PD costs were typically about (US\$) 78, ranging from 58 to 96 depending on fluid volume and bag exchanges. The cost of a single HD session was obtained from the hospital's accounting system and market prices were applied when PD costs were evaluated.

All the transplantations in study patients were performed at Helsinki University Hospital. The cost of transplantation procedure was assessed to be (US\$) 5150 and the costs for inpatient care at surgical ward were 756 per day. Typically, the postoperative hospitalization in Helsinki lasted for three weeks.

The number of days in hospital and visits to outpatient clinics at Tampere University Hospital and at other hospitals were counted. Costs for hospitalization and outpatient visits contain expenses for maintenance, meals, salaries of personnel

and capital costs but cost for laboratory tests, medicines and examinations were excluded since they were assessed as separate categories. For instance, cost for one day hospitalization at the general ward in the TaUH was (US\$) 226 and specific figures were applied for costs for intensive care and cardiac care units as well as for other hospitals.

The patients' medication was recorded and market prices were used in assessing costs. Intradialytic medicines, outpatient prescription drugs and parenteral medicines administered during hospitalization were included in the analysis. The number of operations and invasive interventions were recorded. Specific figures for costs of individual procedures were given by the hospital's accounting system. Costs for constructing an arteriovenous fistula and for PDCI were taken into account even though they had taken place before the initiation of dialysis.

When assessing costs for transportation, distance between home and hospital were estimated for each patient and the number of visits to hospital and back were registered. Costs were calculated on the basis of taxi costs and the figure (US\$) 0,96 for one kilometer was used in the analysis. Data on costs of laboratory tests taken during the follow-up were given by the Central Laboratory of the TaUH. Radiological and other examinations (clinical physiology, nuclear medicine, pathology) were identified and attributable costs were obtained from the respective units.

4.2.3 Costing procedures in Study IV

Cost analysis in Study IV included cost for possible preoperative outpatient visit, cost of the PDCI procedure, postoperative monitoring and hospitalization from the provider's perspective. Unlike in Studies I to III, costs for patients' medication, transportation or laboratory tests were not evaluated in this study. Only costs directly related to PDCI were included. Costs were both collected and reported in Euros in 2010.

4.2.4 Laboratory test evaluation (Study III)

Association between levels of serum mineral metabolism markers, CRP and albumin with costs were evaluated in study III. All measurements of serum total and ionized calcium, PTH, phosphorus, albumin and CRP taken at TaUH during the follow-up were obtained retrospectively from the hospital's database. These

parameters were routinely measured four times in a year (once in three months) and, based on the decision of clinicians; supplementary tests were drawn when needed.

To compare costs between patients with different mineral metabolism status, patients with near-optimal (as defined in K/DOQI recommendations in 2003) (National Kidney Foundation 2003) mineral metabolism levels were identified. In these subjects, Ca and P averaged in between 2,1–2,4 mmol/l and 1,1–1,8 mmol/l and at least one in-target PTH had been measured during the follow-up. Other subjects were defined as having a non-optimal mineral metabolism level.

4.2.5 Mean costs, effectiveness and cost-effectiveness (Studies I–III)

Total costs for each patient were calculated by adding up all the costs generated in separate categories (dialysis therapy, hospitalization, medication etc.) during the follow-up and average daily costs were obtained by dividing total costs by the respective number of days.

In Studies I and II mean costs in different modalities (HD, PD, TX) were separately evaluated for different periods (first six months, second six months, second year etc.). The figures were computed by adding up patients' cost in a given period, dividing the sum by the total number of days in a respective period and finally multiplying the result by the length of the period. In Study III, single patient's average daily costs were applied in the analysis. Discounting was not applied in any of the studies.

Effectiveness was evaluated in Study II and in this analysis, it was determined as a probability to survive a given period (years 1, 2 and 3). Cost-effectiveness ratios were obtained by dividing average cumulative costs during the observation period by respective effectiveness. Since characteristics between patients on HD and on PD were remarkably different, patients on PD were matched with a control-case on HD with similar comorbidities and age (± 6 years). 68 eligible HD–PD-patient pairs were found and CERs for this subpopulation were further determined.

4.2.6 Strategies in determining censoring of the follow-up (Study II)

Since dialysis patients frequently have to change treatment modalities over the course of time, four different strategies were applied to determine the cut-points of follow-up:

Strategy 1. Intention to treat: patients starting dialysis treatment were followed until death or end of follow-up and modality changes were ignored.

Strategy 2. Death of modality: as in strategy 1, patients were followed until death or end of follow-up but technique failure was also considered as death.

Strategy 3. Time on dialysis: As in strategy 1, but follow-up was censored also in transplantation.

Strategy 4. Time on primary modality: follow-up was censored in any change of primarily selected modality.

4.2.7 Peritoneal dialysis catheter-related complications and technique failures (Studies I, II and IV) and grouping of patients (Study IV)

Complications were classified as infectious (peritonitis and catheter infections) and non-infectious (malfunction, leakage, inadequate dialysis and other) complications and they were considered early and late depending whether a complication occurred within 30 days or more than 30 days after the procedure. Technique failure was defined as a switch from one dialysis modality to another due to infectious complications, mechanical problems or inadequate dialysis.

In Study IV, patients who were electively admitted to PDCI were defined as inpatients and those who had their catheter placed on an outpatient basis were classified as outpatients, respectively.

4.2.8 Statistical analyses

Values are expressed as number (percent) or mean (\pm standard error of the mean; SEM or standard deviation; SD). When comparing continuous variables between different groups, Student's t-test was used and Spearman's chi-square test was utilized between categorical variables. In Study III, comparisons between groups were made by Levene's test for equality of variances. Two-sided P values of less than 0.05 were considered to indicate statistical significance.

Survival was estimated by using the Kaplan–Meier method and survival between modalities was compared by using the log-rank test. In Study I survival was defined on the basis of death and censoring was considered when the patient reached the end of the study period or moved to another district. In Study II, survival and censoring were determined as in Study I but additional analyses were conducted as stated in paragraph 4.2.6. In these analyses modality changes were

considered as censoring and technique failure was defined as death. In Study IV, patient survival was defined by death and censoring in the end of follow-up and when a patient withdrew for modality change. Catheter survival was defined by technique failure. End of the follow-up, transplantation and death were considered as censoring. Complication-free survival was defined on the basis of emerging of first catheter-related complication.

In Study III, correlations between continuous values were assessed using Spearman's correlation coefficient and Pearson's correlation coefficient was used for nonparametric data. SPSS (SPSS Inc., Chicago, Ill., USA) was utilized for controlling for clinical characteristics (age, body mass index, gender, dialysis modality and primary renal disease). Survival was not evaluated in Study III.

5 RESULTS

5.1 Costs and structure of costs in HD, PD and TX (Study I)

The average treatment costs in different modalities were separately assessed for the first six months, months 7–12, second year and third year. Results are shown in Table 8 and Figure 2. Due to great costs of the transplantation procedure and the subsequent postoperative hospitalization and close outpatient visits, costs (US\$) for the months 0–6 were high (38 265) in TX patients compared with HD and PD (32 566 and 25 504, respectively). After the first months, costs in TX group lowered markedly whereas they were rather stable in HD and PD. There was a trend of lower costs in PD compared with HD during all the observed periods but the difference was statistically significant only in the first six months.

In the dialysis modalities, approximately half of the total expenditures were caused by the dialysis therapy itself (45–56% in HD and 51–61% in PD, respectively). The absolute figures were almost identical between the two modalities. Costs for hospitalization were the second largest item and in the first six months they accounted for 25% of total costs in HD and 27% in PD. During years 2 and 3 costs for hospitalization decreased being 14–18% of total costs. The medication costs remained rather stable during the follow-up and they were in between 9–13% of total expenditures in HD and 5–8% in PD. Costs for transportation accounted for 9–10% of costs in HD whereas in PD they were only marginal. Together, costs for dialysis therapy, hospitalization and medication explained 79–88% of total costs. Average costs were separately evaluated in different subgroups. In patients with non-primary renal disease costs were slightly higher than in patients with primary renal disease, both in HD and in PD. Also, the average costs in diabetics seemed to be higher than in non-diabetics. There were only nine patients below 50 years who remained on HD for more than one year. In those patients the average second year costs were 75 448 compared with 52 876 for patient aged 50 years or more. Contrary, in PD the second year costs were 39 662 in those below 50 years and 49 137 among patients over 50 years.

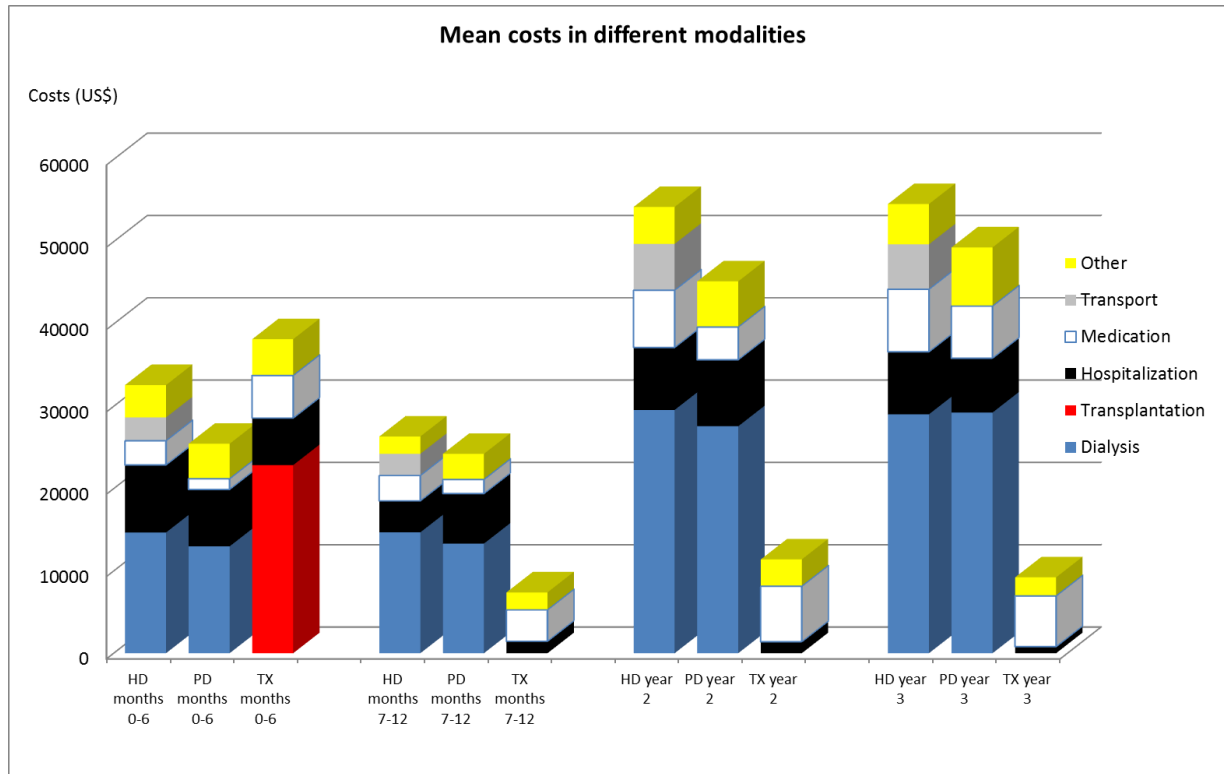
In TX patients, the costs for transplantation were on average 22 900 per patient. All the transplantations in the study were cadaveric. After the transplantation

procedure was performed, annual total costs were between 9 240 and 11 446. Expenses for medication were by far the largest item causing 59–67% of total costs and rest of the costs were divided rather evenly between hospitalization, outpatient control visits, laboratory tests and transport. Costs for the first six months were at about the same level both in men and women, in diabetics and in non-diabetics and in those below and over 50 years. Also average second year costs for these subgroups were close to each other.

Table 8. Mean costs in different treatment modalities

		Months 0–6	Months 7–12	Year 2	Year 3
HD	Mean (\pm SEM)	32 566 (\pm 1093)	26 272 (\pm 1149)	54 140 (\pm 3459)	54 490 (\pm 3650)
	Number of patients	138	95	61	31
	95% confidence interval for mean	30 402–34 730	23 986–28 558	47 222–61 058	47 044–61 936
PD	Mean (\pm SEM)	25 504 (\pm 1094)	24 218 (\pm 1685)	45 262 (\pm 3338)	49 299 (\pm 2963)
	Number of patients	76	53	27	12
	95% confidence interval for mean	23 327–27 681	20 832–27 604	38 819–52 505	42 840–55 758
TX	Mean (\pm SEM)	38 265 (\pm 2043)	7420 (\pm 669)	11 446 (\pm 1316)	9240 (\pm 464)
	Number of patients	55	49	43	33
	95% confidence interval for mean	34 179–42 531	6075–8756	8788–14 104	8298–10 182
Ratio	PD/HD	0,78	0,92	0,84	0,90
Ratio	TX/HD	1,17	0,28	0,21	0,17

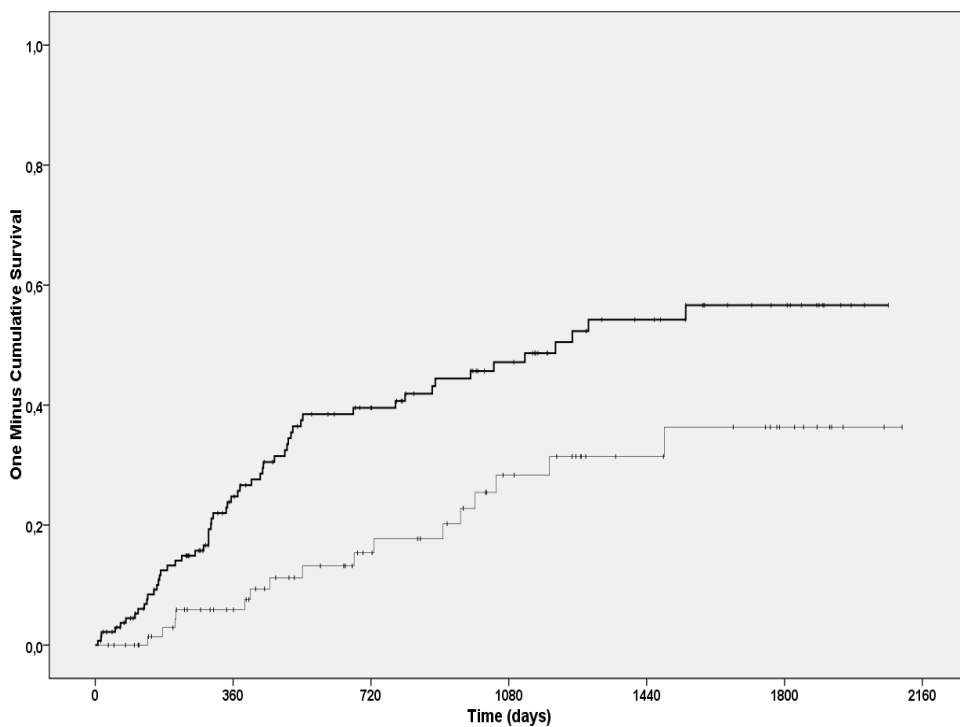
Figure 2. Mean costs and distribution of costs in different treatment modalities



5.2 Patient survival (Studies I and II)

During the study period, 34% of all patients died and for all patients, the cumulative survival rates for 1, 2 and 3 years were 0,81, 0,68 and 0,60, respectively (Figure 3). The median survival time was 58 months. Mortality rates in HD and PD were 41% and 21%, respectively. Compared with HD, survival on PD group was better ($p = 0,0025$). The difference was statistically insignificant when technical survival was taken into account and considered as death ($p = 0,58$). Cardiovascular causes accounted for more than a half of deaths.

Figure 3. Patient survival (Studies I and II) by Kaplan–Meier method on HD (thick line) and PD (thin line). $P = 0.0025$ by the log-rank test



5.3 Modality changes (Studies I and II)

Of 76 patients starting with PD, 27 patients (36%) had to change modality to HD due to treatment failures. Nineteen of the changes occurred during the first year and the most common reason for failures was recurrent peritonitis episodes. The combined rate of peritonitis and catheter infection was one episode per patient per 18 months. Changing from HD to PD was uncommon. There were 12 HD patients out of 138 who voluntarily transferred to PD, and no treatment failures occurred in HD patients. Fifty-five patients (26%) received a TX during the study period, 29 of them started with HD and 26 were treated on PD (21% of HD patients and 34% of PD patients, respectively, $p=0,051$). All the transplantations were cadaveric and mean age in TX patients at the time of transplantation was approximately 45 years. The average transplantation rate was 21 pmp per year (region population 440 000).

5.4 Cost-effectiveness of HD and PD (Study II)

CERs were calculated separately for year 1, year 2 and year 3 in both dialysis modalities. Cumulative figures for the first three years are presented in Table 9, Different strategies were applied to determine the cut-points of observation. Of four different strategies to assess cost-effectiveness of dialysis therapies, PD dominated in three. The only exception was the strategy in which technique failure was considered as death. In this approach, incremental costs exceeding US\$ 444 000 were incurred to achieve an extra life-year in HD.

In the subpopulation of 68 matched HD–PD-patient pairs, mean age of the patients was 53,9, equally on HD and on PD. No statistically significant differences in prevalence of diabetes ($p=0,205$) or transplantation rate ($p=0,466$) were found. CKD was caused by primary renal disease (chronic glomerulonephritis, interstitial nephritis or polycystic kidney disease) in 31 patients on HD and 29 patients on PD ($p=0,863$). There was no statistically significant difference in number of deaths (26 on HD and 16 on PD; $p=0,095$) but survival of PD patients was better compared with patients on HD ($p=0,025$ by the log-rank test). The first three-year period costs and effectiveness are shown in Table 10. CERs for the whole population and for the subpopulation were close to each other. When cumulative first three years' ICERs were evaluated, PD dominated in three out of four strategies – likewise it did in the entire study population. PD also dominated in most observations, when

individual years were separately analyzed within these three strategies. When technique failure was considered as death, ICER on HD was US\$ 218 610.

Table 9. Cost-effectiveness ratios for first three years on HD and PD for the whole population in different strategies to determine the cut-points of observation. Costs: cumulative costs in three years; effectiveness: probability to survive the three-year period.

	Cost in HD (US\$)	Cost in PD (US\$)	Effectiveness in HD	Effectiveness in PD	CER in HD	CER in PD	Incremental costs in HD	Incremental effectiveness in HD	ICER in HD
Strategy 1: Intention to treat	165 712	143 559	0,53	0,72	313 552	200 278	22 153	-0,19	PD dominates
Strategy 2: Modality survival	165 712	137 249	0,53	0,46	313 552	295 540	28 463	0,06	444 041
Strategy 3: Time on dialysis	180 125	165 848	0,45	0,52	396 489	320 975	14 277	-0,06	PD dominates
Strategy 4: Time on primary modality	185 021	158 853	0,39	0,53	471 872	298 428	26 168	-0,14	PD dominates

Table 10. Cost-effectiveness ratios for first three years on HD and PD for matched HD–PD-patient pairs in different strategies to determine the cut-points of observation. Costs: cumulative costs in three years; effectiveness: probability to survive the three-year period.

	Cost in HD (US\$)	Cost in PD (US\$)	Effectiveness in HD	Effectiveness in PD	CER in HD	CER in PD	Incremental costs in HD	Incremental effectiveness in HD	ICER in HD
Strategy 1: Intention to treat	165 678	144 510	0,57	0,71	289 647	203 822	21 168	−0,14	PD dominates
Strategy 2: Modality survival	165 678	138 155	0,57	0,45	289 647	309 695	27 523	0,13	218 610
Strategy 3: Time on dialysis	187 584	165 941	0,47	0,52	402 368	322 090	21 643	−0,05	PD dominates
Strategy 4: Time on primary modality	194 941	158 703	0,37	0,53	520 259	301 259	36 238	−0,15	PD dominates

5.5 Association between treatment costs and levels of serum calcium, phosphorus, PTH, albumin and CRP (Study III)

In this study 109 patients were included in the analysis. Average daily treatment costs (US\$) were 161 and median costs were 151. Mean serum levels (\pm SD) for serum total Ca, ionized Ca, P and PTH were 2,4 (\pm 0,13) mmol/l; 1,3 (\pm 0,05) mmol/l; 1,7 (\pm 0,37) mmol/l and 16,8 (\pm 18,7) pmol/l. In 71% of patients average PTH was below the level recommended by K/DOQI in 2003 (16,5 pmol/l) and exceeded the upper limit (33,0 pmol/l) in 15% (National Kidney Foundation 2003). According to PTH level, patients were divided into three subgroups: In 59 patients PTH was constantly below target; in 43 patients there was at least one result between the recommended levels. In 7 patients PTH was continuously elevated. Average daily costs in the low-PTH group were 170 (\pm 48) whereas in patients with one or more PTH in-target, costs were 148 (\pm 31), the difference was statistically significant ($p=0.01$). Average costs were 172 (\pm 85) in the patients with high-PTH and compared with the in-target group, statistically significant difference was not reached ($p=0,18$).

Altogether 19 patients with near-optimal mineral metabolism levels were identified. Average daily costs in patients with near-optimal levels were 145 (\pm 31). In those 90 patients with non-optimal levels, mean costs were 165 (\pm 48). The difference did not achieve statistical significance ($p=0,095$). Patient characteristics between near-optimal and non-optimal groups did not significantly differ from each other.

Relationships between costs and given laboratory parameters were determined after controlling for patients' characteristics. Results are shown in Table 11. Statistically significant positive correlation was found between costs and CRP whereas costs and albumin were inversely correlated. No significant correlation between costs and mineral metabolism markers was noticed. A weak negative correlation between costs and PTH, which was noted in non-controlled data turned out to be insignificant after controlling for characteristics.

Table 11. Correlation coefficients between average daily costs and laboratory parameters after controlling for patient characteristics

	Costs	PTH	Ca	Ionized Ca	P	Albumin	CRP
Costs	1,000						
PTH	-0,1369	1,000					
Ca	0,0274	0,2004*	1,000				
Ionized Ca	0,1379	0,0841	0,6226**	1,000			
P	-0,0230	0,1575	0,2654**	0,0574	1,000		
Albumin	-0,4680**	0,1118	0,3287**	0,0361	0,1903	1,000	
CRP	0,3251**	0,0602	0,0689	-0,0087	0,0054	-0,3785**	1,000

*p <0,05 (2-tailed); **p <0,01 (2-tailed)

5.6 Costs and outcomes in inpatient and outpatient peritoneal dialysis catheter insertion (Study IV)

Of a total of 106 PDCIs, 46 were in electively admitted patients (inpatient group) and 41 catheters were placed on an outpatient basis (outpatient group). In 19 cases PDCI took place during hospitalization for other medical reasons (other group). Mean ages in inpatient, outpatient and other groups were 52, 53 and 63 years, respectively. No significant differences in characteristics (gender, body mass index, cause of ESRD) between outpatient and inpatient subjects were found.

The number of early complications was 23 (22%), 13 of them were infectious. An immediate postoperative complication occurred in four cases, none of them was life-threatening and hospitalization over 48 hours was not needed. Within 90 days, the cumulative rates of technique failure, infectious complication and any complication were 10%, 25% and 38%, respectively. Differences in incidences of complications were not statistically significant between inpatient and outpatient groups but a trend toward a lower rate of infectious complications in outpatients was noted (p=0,080).

During the entire follow-up, the incidence rates of technique failure and peritonitis were 1 per 41 months per patient and 1 per 18 months per patient. Overall catheter survival for one, two and three years was 72%, 60% and 52%, respectively. All-cause mortality rates one, two and three years were 18%, 25% and 38%, respectively.

Mean PDCI-procedure related hospitalization time was 2,67 days in inpatients. Three patients in the outpatient group were briefly hospitalized because of immediate postoperative complications and the average length of hospital stay days in the entire group was 0,098 days. Total costs of the PDCI process are shown in Table 12. Compared with the inpatient group, total average costs (\pm SEM) (EUR) were significantly lower in the outpatient group (1346 ± 33 vs. 2320 ± 142 , $p < 0.000$).

Table 12. Total average costs (EUR) per patient of the peritoneal dialysis catheter insertion process

	Inpatient group	Outpatient group
Preoperative outpatient visit	0	119
Peritoneal dialysis catheter insertion procedure	833	833
Postoperative monitoring (recovery room)	0	340
Hospitalization (mean) (EUR 556/day)	1487 (2,67 days)	54 (0,098 days)
Total (mean) (\pm SEM)	$2320 (\pm 142)$	$1346 (\pm 33)^*$

* $p < 0,000$ compared to inpatient group

6 DISCUSSION

6.1 Costs and distribution of costs in dialysis modalities (Study I)

Total annual healthcare costs in Studies I and II were on the average somewhat more than US\$ 50 000 on HD and a little less than 50 000 on PD and cost on HD were 8-27% higher than costs on PD. HD patients in the studies were treated solely with CHD. These results are pretty close to figures in other reported studies. Interestingly, in studies which have been conducted in developed countries, CHD to PD ratio seems to have remained at about the same level from the 1980s to recent years – regardless of perspective (Churchill et al. 1984; Smith and Wheeler 1988; Nebel et al. 1991; Coyte et al. 1996; Haycox and Jones 1996; Sennfalt et al. 2002; Shih et al. 2005; Berger et al. 2009; Haller et al. 2011). Distribution of costs was also found similar to other studies, dialysis therapy itself caused approximately half of costs and of the rest; costs for medication and hospitalization were the largest items (Goeree et al. 1995; Bruns et al. 1998; Lee et al. 2002; Grun et al. 2003). Differences in the total healthcare costs between PD patients and HD patients in our study were largely attributable to differences in the cost for transport and, to a lesser extent, to higher costs for medication in HD patients. The reason for a difference in transportation costs between the groups is obvious; patients on HD visit hospital three times in a week whereas patients on PD have their outpatient controls only once in four to eight weeks.

Higher costs were found in patients with diabetes and non-primary renal disease compared with non-diabetics and those with primary renal disease both in HD and in PD. An advanced age does not necessarily increase costs in HD patients whereas in PD costs were higher in patients aged 50 years or over compared with younger ones. However, due to relatively small number of patients and, especially, differences in modality selection and comorbidities, the impact of confounding factors is difficult to eliminate.

6.2 Costs, distribution of costs and survival in kidney transplantation (Study I)

In transplantation surgery, plenty of resources are required. A successful operation necessitates highly-educated surgeons and personnel, close pre-, peri- and postoperative monitoring and a tertiary level hospital with an adequate infrastructure. Consequently, costs for transplantation procedure are high and costs in TX patients during the first months exceed costs in dialysis patients. After that, costs decline sharply. In Study I, costs for TX were no more than 17%–31% of costs for dialysis after the first six months. Costs for medication accounted for more than half of total costs, most of which were induced by immunosuppressive compounds. The figures are parallel with results reported by Hu et al. They found that the high initial costs for CTX were shortly balanced and the total cumulative costs for CHD and CTX were equal by 18 months and after that they were lower for CTX (Hu et al. 1998). In several other studies costs for second year and thereafter in TX patients are less than half of the costs in dialysis patients (Laupacis et al. 1996; Erek et al. 2004; Haller et al. 2011; Villa et al. 2011; Rocha et al. 2012). If a graft is lost before a certain time and the high initial costs for transplantation procedure have not been counterbalanced by lower costs of maintenance immunosuppressants compared with dialysis therapies, TX will even cost more money. Length of this period has been found to vary between 1,5 and 4,6 years, depending on the structure of costs in different health care systems (Hu et al. 1998).

Total treatment costs in TX patients between different subgroups in Study 1 were at about the same level. Advanced age or prevalence of diabetes did not seem to significantly affect costs. This result was confirmed by Wong et al. They concluded that transplanting the younger and healthier individuals with end-stage kidney disease maximises survival gains and saves money. Listing and transplanting those with considerable co-morbidities is also cost-effective and achieves substantial survival gains compared with the dialysis alternative. Preferentially excluding the older and sicker individuals cannot be justified on utilitarian grounds (Wong et al. 2012). On the other hand, in most elderly patients with markedly limited life-expectancy, TX is not rational. Given the high rate of TX-related complications associated with increased age and with cardiovascular diseases and, on the other hand, the very limited effect of TX to produce incremental life-years among the most elderly and among those with high burden of comorbidity, the cost-effectiveness of kidney transplantation in the elderly is questionable.

Especially, when the waiting time is more than two years, the survival advantage has been found to decrease dramatically. A Canadian study suggested that, economically taken, transplantation is attractive for well selected patients below 70 years in centers with waiting times less than two years and for patients up to 80 years when LTXs are available (Jassal et al. 2003). Conclusively, if the time from the initiation of dialysis to the transplantation can be reduced, both survival may be increased and costs may be decreased. To minimize patients' waiting time, processes which facilitate acceptance to transplantation should be implemented during pre-dialysis and dialysis time. Tests and examinations required as pre-transplantation evaluation should be systematically scheduled to avoid unnecessary delay.

Superiority of TX over dialysis therapies – both economically and medically – has been shown in numerous other studies. Vast majority of studies have reported a survival advantage in TX patients compared with dialysis. The only exception might be intensive HHD which effectively restores disturbed homeostasis in uremic patients. Similar death rates among HHD and CTX have been reported in a recent study (Pauly et al. 2009). HRQOL was not evaluated in Study 1, but higher scores in TX patients compared with dialysis patients have commonly been found in previous studies (Russell et al. 1992; Laupacis et al. 1996; Park et al. 1996). Nevertheless, results in studies comparing HRQOL in TX with dialysis may be affected by different patient populations at varying intervals of treatment sometimes without regard to comorbidity or mortality (Laupacis et al. 1996). Results of Study 1 corresponded with the general and practically unanimous opinion that TX is the treatment of choice for most patients with ESRD, also among the elderly patients.

Pre-emptive kidney transplantation is defined as transplantation prior to dialysis therapy – at the time when renal function has not yet declined below critical level. Compared with conventional policy (TX after dialysis), pre-emptive TX offers certain benefits: Accelerated atherosclerosis and vascular calcification attributed to dialysis may be avoided and survival of pre-emptive TX patients has been found superior compared with those who receive their transplants after initiation of dialysis therapy (Raggi et al. 2002). However, bias may be caused by patient selection: pre-emptive TX patients are more likely to be younger and more educated compared with those TX patients who have been treated with dialysis (Kasiske et al. 2002).

6.3 Cost-effectiveness of HD and PD (Study II)

From an economic standpoint, HD and PD can be considered as clinically equivalent modalities and given this near-equivalence, cost issues become the major driver in making health economic decisions (Rosner 2013). It is important to acknowledge the distinctive character of dialysis therapy. Apart from certain diseases in which medication or a single operation may restore patient's health, dialysis does not provide cure for kidney disease but it is an expensive technology that is regularly needed and it maintains a patient in a state of dependency (Stanton 1999).

While selection between HD and PD is not random and modality switch is common, comparison between the modalities is complex. Frequently, modality changes are caused by medical reasons which are related with additional treatment costs. It has been suggested that cost-effectiveness of ESRD treatments should primarily be evaluated at an aggregate level before considering specific modalities (De Wit et al. 1998). Nevertheless, if the purpose is to compare between the modalities, the impact of modality changes has to be taken into account. Few studies have thoroughly discussed the importance of modality changes on costs. In Study II, four alternative strategies were decided to apply in determining the end-points of observation:

In strategy 1 (intention-to-treat), modality changes were ignored. Patients who started on PD were classified as PD patients regardless of modality changes and those who started on HD belonged to the HD group. In this analysis, patients with functioning TXs are included and both in HD and PD, CERs decreased year after year. For the first three years, cumulative costs were lower and effectiveness was better on PD, compared with HD for obvious reasons: patients on PD were younger and, compared with patients on HD; a greater proportion received a transplant.

In strategy 2 (modality survival), technique failure was considered as death. There were no failures in HD patients but in the PD group effectiveness lowered clearly compared with strategy 1. Subsequently, CER for PD was much higher than it was in strategy 1 and from this perspective, PD did not dominate as it did in strategy 1. Instead, more effectiveness was gained with HD but the ICER was over US\$ 444 000, which is not cost-effective.

In strategy 3 (time on dialysis) follow-up was censored in transplantation. Contrary to strategy 1, since time after transplantation is not included, CERs did not decrease but they remained rather stable (HD) or increased slightly (PD) year

after year. As cumulative three-year costs were lower and survival was better in the PD group, PD dominated over HD.

In strategy 4 (time on primarily selected modality) follow-up was censored in any modality change. Again, PD was found to dominate. CERs in both modalities were pretty close to figures in strategy 3, in which modality changes – voluntary or due to failures – were included. Apparently, modality changes from PD to HD due to failures did not seem to have any major effect on costs. In HD patients CER was even lower in strategy 3 than in strategy 4; changing voluntarily from HD to PD in eligible patients may decrease costs. Contrary to a report from the United States (Shih et al. 2005), failures did not have any major impact on costs, but in that analysis costs were evaluated at the aggregate level and costs for individual patients with technique failure were not assessed separately. The result is in line with a Canadian study, which found similar costs in patients with HD-only and patients with a PD failure (Chui et al. 2012). Nevertheless, it is obvious that strategies which reduce involuntary modality switching may help in lowering treatment costs.

PD dominated in three out of four strategies and in one strategy, the ICER of HD clearly reached values beyond the indistinct limit of cost-effectiveness. Nevertheless, concluding that all HD patients should be transferred to PD to achieve savings is not correct. Instead, we can state that patients on PD had been appropriately selected and they succeeded in their modality. Opting out of the modalities is a complex decision and it is of great significance to choose a modality which is the most suitable for the particular patient.

There were differences in characteristics between patients on HD and PD and comparisons between the groups may be distorted and favor PD. To minimize the effect of selection bias, a subgroup of patients with similar characteristics were assessed separately. Sixty-eight matched HD–PD pairs were identified and further selected in the analysis. In the matched subgroup, no statistically significant differences in mean ages or comorbidities were found between HD and PD patients but in a historical cohort study, controlling for necessary variables may be insufficient and distortion is difficult to avoid. In the subgroup analyses survival was superior in PD patients compared with patients treated with HD. CERs and ICERs were very close to the results in the entire population. Interestingly, compared with all HD patients, costs and effectiveness in the subgroup were almost identical. Indirectly, it can be concluded that treating older patients with HD causes similar costs than treating younger patients.

While mortality among dialysis patients is high, effectiveness was not defined as the mean of gained life-years, as it usually is. Instead, survival for individual years

was evaluated. Thus, CERs in this study were calculated by, first, considering the amount of money invested in a certain population in a given period and calculating patients' mean costs, then, by counting the portion who actually reached the pre-determined end-points and, finally, by dividing the mean costs by the probability of surviving.

Cost data derive from 1997 and treatment protocols have changed and actual production costs have remarkably increased since then. Patients on HD were treated solely with CHD or SatHD. There were not patients on HHD and neither HF-HD nor HDF – modalities which are frequently exercised today – were provided during the study period. Almost all PD patients were treated with CAPD and APD comprised only 4,2% of all PD days. Since consumption of dialysis fluids and treatment related equipments is high in APD, it can be estimated that APD induces about 40% more costs than CAPD. Costs for hospitalization and transport have grown and prescribing expensive medications such as erythropoiesis stimulating agents, non-calcium based P binders and cinacalcet has become a routine. However, intensification of dialysis therapy has occurred both on HD and PD, indications for hospitalization have not remarkably changed and the use of expensive medications has increased similarly in both modalities. Subsequently, even though the present costs of dialysis treatment cannot be exactly derived from the results of these studies, the ratio between HD costs and PD costs probably may have not prominently changed. Whether effectiveness in the modalities has changed in these years, remains unanswered. Indirectly, three-year mortality among PD patients in Studies I and II in the 1990s was pretty close to three-year mortality rate in Study IV (38%) (study period 2004–2009) and rates in technical failures were also close to each other. Older patients with several comorbid conditions are accepted to enter RRT. The mean age of PD patients in Studies I and II was 51 years whereas it was 55 years in Study IV. It can be suggested that, at least in PD, the outcomes of treatment have remained comparable to the previous years despite treating older and sicker patients.

6.4 Dialysis modality selection

In comparing between HD and PD, an issue of critical importance is the fact that patients are not randomly assigned to a given modality. ESRD patients' life-tracks on RRT are not limited to a single modality. The clinical needs during the time course change and the most suitable modality is determined on the basis of medical

conditions, complications and patient's choice. Frequently these needs are better managed by sequential use of different modalities (Shih et al. 2005). From patients' viewpoint, cultural factors, employment, and societal issues play an important role in modality selection and they also impact on treatment costs. Worldwide, PD and HHD are underrepresented and CHD is overrepresented as an initial modality. Modality switching is common, both for medical and non-medical reasons. Therefore, timing of a study comparing modalities becomes a critical variable in itself. HHD and PD have a high drop-out compared with CHD and studies assessing costs and HRQOL later in the course of treatment can be biased: successful and satisfied survivors in modalities are studied (Kurtin and Nissenson 1993).

Most people entering into RRT are eligible both for HD and for PD (Mendelssohn 2009) but after having started the treatment a remarkable portion of PD patients will experience a technique failure. There are no means to reliably predict which patients will success on PD and which patients will fail and how does the failure impact on treatment and prognosis. Whether more aggressive PD-first policy will result in greater PD technique failures rates is unknown (Chui et al. 2012). However, similar failure rates have been reported in Hong Kong, where 80% of patients are treated with PD and in the United States with 7% patients on HD (Chaudhary et al. 2011). Due to multiple differences between patient populations and setting, the Hong Kong experience cannot be universally generalized but, at least, a higher utilization of PD do not deterministically result in higher rate of treatment-related complications. It has been suggested that 20–40% of dialysis patients in the United States could be treated with PD (Jiwakanon et al. 2010) and savings over US\$ 1,1 billion were gained in 5 years on Medicare costs if PD allocation were increased from current 7% to 15% (Neil et al. 2009).

Several reasons contribute to the underutilization of PD. In the United States it has been argued that the increased numbers of in-centre HD units, physician comfort with the modality, perceived superiority of HD, and reimbursement incentives all affect this disproportionate assignment between modalities and also a higher transplantation rate among patients treated with PD and the transfer from PD to HD partly explain the low PD prevalence (Chaudhary et al. 2011). Most of these reasons can be generalized to other developed countries as well.

Reimbursement structure is acknowledged the most important non-medical factors in modality selection (Nissenson et al. 1993; Nissenson et al. 1997) and by deciding to treat patients with highly-reimbursed dialysis modality, financial profits can be generated by dialysis providers. Among financial incentive mechanisms to

encourage the utilization of most cost-effective dialysis modalities, profit neutrality is of crucial importance (Cleemput and De Laet 2013).

In Studies I and II the proportion of patients starting with PD was 36% whereas in 2012, 24% of patients in Finland started their RRT on PD. In a modality selection process, several factors contribute to the decision. Compared with patients on HD, PD patients in Studies I and II were younger, the cause of kidney failure was more often chronic glomerulonephritis or insulin-dependent diabetes mellitus and a smaller proportion suffered from symptomatic coronary artery disease. Due to the baseline differences in characteristics, survival between the groups was also different. Mortality rates were higher in HD patients than in PD patients (41% vs. 21%). Poorer survival is associated with high treatment costs: Patients with the highest risk of death are usually treated in hospital, they need extra medication and investigations and despite the efforts, a remarkable percentage will die. Selection also affects transplantation rate. Patients treated with PD were more likely accepted on TX waiting list and altogether 34% of them were eventually transplanted compared with 21% of patients on HD. The difference in TX rates between the groups did not quite reach statistical significance but was pretty close. Due to the high TX rate, many potential treatment failures can be avoided. Differences between patient characteristics, survival and TX rate all contribute on treatment costs and, subsequently, the groups are different in their cost expectations already from the beginning of the RRT. Due to potential effect of several difficult-to-measure factors affecting modality selection, ideally a randomized controlled trial would be essential to evaluate the true difference in treatment efficacy between modalities – a trial which is most unlikely to be conducted for clinical reasons.

6.5 Survival in dialysis

In Studies I and II the overall three-year survival was 60%, which is close to survival rates in current large studies (Weinhandl et al. 2010; Collins et al. 2013) and survival of patients has even continuously improved in Finland in recent years (http://www.musili.fi/files/1280/Munuaistautirekisteri_vuosiraportti_2012.pdf)

Not surprisingly, mortality in patients aged 15 to 39 years was much lower than it was in patients over 55 years (11% vs. 42%) Contrary to recent reports, mortality among patients on HD was statistically significantly higher than on PD patients. Remarkable differences in patient characteristics possibly explain the difference

and instead of survival advantage provided by PD, we can conclude that those patients who will survive better are offered PD as the first modality.

Universally, mortality among dialysis patients continuously remains much higher than mortality among the general population. Especially incidence of cardiovascular events is manifold compared to non-CKD patients. The likelihood of five-year survival on dialysis for a patient aged 60 years does not exceed 50% and probability to survival is at about the same level than that of a similar aged woman with ovarian carcinoma (Akhtar-Danesh et al. 2012). Furthermore, an ovarian cancer survivor is likely to have been cured after five years whereas dialysis patients' risk of death continues without attenuation (Hutchison 2009).

An increased dose of dialysis enhances clearance of solutes and it is tempting to theorize that improved homeostasis would result in better outcomes. Unfortunately, only one study has found association between frequent HD and lowered risk of death (Chertow et al. 2010). Among wait-listed patients, intensive treatment of uremia with HHD may help in limiting the negative impact of prolonged waiting time on outcomes after transplantation and may also offer survival advantage for those patients who may never be transplanted, e.g. immunologically highly sensitized and those with recent cancer or other prohibitive medical comorbidities (Pauly et al. 2009). There were no HHD patients in Studies I and II but in other studies lower costs (De Wit et al. 1998; Klarenbach et al. 2013) and better HRQOL (Finkelstein et al. 2012; Hall et al. 2012) have generally but not uniformly (Lee et al. 2008) been reported.

In CKD patients, late referral to nephrologists has been found to be associated with increased morbidity and mortality (Arora et al. 1999) and in a Canadian simulation analysis, early referral resulted in cost-savings and improved patient survival. The potential benefits of early referral include identifying and managing coexisting conditions associated with CKD which may accelerate decline in renal function and optimizing the biochemical, physical and psychological state of the patient during predialysis period. (McLaughlin et al. 2001).

6.6 Levels of mineral metabolism markers and costs (Study III)

Disordered concentrations of mineral metabolism markers in dialysis patients are associated with an increased risk for soft tissue and cardiovascular calcifications (Block et al. 1998; Block et al. 2004) and elevated PTH and P have been found to

associate with high costs for hospitalization. In Study III, no significant correlations between treatment costs and serum Ca, P or PTH were found.

Patients' blood tests had been drawn as a part of normal treatment. Routinely, mineral metabolism tests were taken once in three months. As additional tests were taken when needed and values may vary over time, average values in individual patients may be distorted and cause misclassification. More importantly, the distribution of PTH values was not even. Patient data was processed in 2006 and in defining targets, K/DOQI recommendations (National Kidney Foundation 2003) were applied. In most patients (54%), PTH was constantly below the suggested level 16,5 pmol/l. In only seven patients the average PTH was constantly elevated. Mean costs in low-PTH patients were statistically significantly higher compared with in target-PTH patients, but after controlling for patient characteristics, no correlation between PTH and costs was found. Additional analyses comparing in-target serum Ca level with non-optimal serum Ca and in-target serum P level with non-optimal P were conducted and no significant differences in costs were present. Of 109 patients, near-optimal mineral metabolism levels were found in only 19 patients. Near-optimal was defined in a pretty liberal way: mean serum Ca and P in K/DOQI targets and of all PTH measurements, at least one was between 16,5-33,0 pmol/l.

A relatively small number of patients in Study III restricts interpretation of results. As the total number of patients was 109 and there were subgroups with only seven individuals, achieving any statistical significance between the groups would require definite differences in outcomes. Data were derived from the 1990s and targets and treatment protocols differ from current recommendations. At the time, hyperparathyroidism in dialysis patients were managed by large doses of Ca-based phosphate binders whereas nowadays the amount of elementary calcium is recommended not to exceed 1500 mg in a day (KDIGO 2009). Non-calcium based phosphate binders were not routinely prescribed and paracalcitol or cinacalcet were not available. Parathyroidectomy was also often needed to treat severe hyperparathyroidism.

Both levels of CRP and albumin correlated with costs. Measurement of CRP is a routine procedure when a patient is treated due to infection and correlation of CRP with costs is evident. Elevated CRP was frequently measured in patients with acute infection causing hospitalization and extra costs. In this analysis, laboratory tests taken when needed instead of pre-scheduled protocol, CRP is rather a marker of infection than a marker of chronic inflammation.

Level of albumin was strongly inversely correlated with treatment costs and also with CRP. This finding is consistent with results found in other studies. Hypoalbuminemia resulting from chronic inflammation and malnutrition in dialysis patients is a strong independent predictor of adverse outcomes (Kalantar-Zadeh et al. 2003; De Mutsert et al. 2008). Atherosclerotic cardiovascular disease frequently coexists with chronic inflammation and malnutrition (Fouque et al. 2008).

6.7 Comparing inpatient and outpatient peritoneal dialysis catheter implantation (Study IV)

At TaUH, a structured PDCI protocol has been implemented. The purposes of Study IV were to describe the protocol and to compare short term outcomes and costs between elective inpatient and outpatient procedures. No difference in outcomes or complication rates between the groups was found, numbers of technique failures and complications were surprisingly equal. Immediate postoperative adverse events were mild and out of 109 PDCIs, short-term hospitalization due to complications was required in only four cases.

The incidence of technical failures was higher than reported in other studies. While the first year survival of catheters was 72% in our study, authors from Asian countries have reported figures over 93% (Ouyang et al. 2015; Park et al. 2014). In recent studies from the United States, catheter survival has also exceeded our figures (Singh et al. 2010; Shen et al. 2013) but in older reports from the 1990s, comparable survival rates have been found (Apostolidis et al. 1998; Gadallah et al. 1999). Peritonitis was the most common reason for failure in our study, as has been found in several other studies as well (Schaubel et al. 2001; Nodaira et al. 2008; Jaar et al. 2009). However, policy to remove catheter due to peritonitis seems to vary between centres (Yang et al. 2008). Altogether 90 peritonitis episodes occurred in 58 patients during the study period and peritonitis rate was one episode per 18 months per patient. Both higher (Monteon et al. 1998; Davenport 2009) but mostly lower (Ortiz et al. 2004; Cnossen et al. 2010; Medani et al. 2012; Hsieh et al. 2013) incidence rates have been reported. According to the Finnish Registry for Kidney Diseases, peritonitis rate in Finland was approximately one episode per 24 months per patient in 1998–2003 (486 episodes per 1000 patient-years) (<http://www.musili.fi/files/630/Report2003.pdf>).

In PD, personnel's experience and effective patient training may help in avoiding common treatment-related complications. A careful and aseptic technique

in performing treatment and an early identification of problems may decrease complication rates and the incidence of failures. An association between clinic size and outcomes has been found. In centres with more than 25 (Afolalu et al. 2009) or 50 patients (Plantinga et al. 2009), failure rates have been lower than in smaller clinics.

Costs in outpatient patients – from the provider’s perspective – were significantly lower compared with the inpatient group. The average difference was EUR 974, which is 42% less than costs in the inpatients. Virtually, the importance of perspective became evident in this study: From the provider’s perspective the costs for an outpatient PDCI were clearly lower than in an inpatient PDCI but when costs were calculated on the basis of charges (hospital’s invoices paid by municipalities), an opposite result was found. Cost for inpatient and outpatient procedures were EUR 1864 and 2310, respectively.

Since no difference in outcomes between the groups was found, it can be concluded that an outpatient PDCI is cost-saving and hospitalization for the procedure is not necessary. An outpatient PDCI has been routine in many centres for years but still, many units admit patients. As the demands to reduce hospitalization are increasing due to economic reasons, evidence-based data favouring an outpatient procedure is now provided.

6.8 General aspects on health-economic evaluation

The cost-benefit analysis in economic evaluation of health care have been adapted from the general welfare area and early applications of cost-benefit approach were undertaken in the United States during the 1930s in connection with flood control programs. CBA is regarded as the most comprehensive form of economic evaluation and it undoubtedly is suitable for industrial purposes in which pricing of investments and outcomes is a standard procedure. Thereafter, it has been used in numerous public sector areas such as transport, urban planning and, finally, health care (Robinson 1999). In recent years, studies evaluating cost-effectiveness have become the most popular form of health economic research. The primary focus in early cost-effectiveness studies was a complete assessment of health care budget and to allocate resources as effectively as possible. The resource allocation involves considering the aggregate maximization of outcomes. However, most applications of cost-effectiveness analysis have not evaluated budgets across all interventions. Instead of the question "How money may be spent to most effectively extend

lives?" they have taken a narrower approach and focused on comparing interventions that are viewed as alternatives for a specific medical condition (Gafni et al. 2006; Bridges et al. 2010).

Health and life are not tradable commodities. Thus, rationality of presenting improvements in medical condition as an amount of money or considering one year of complete health and two years in a state of half-dead as equal and interchangeable options appear arguable. Nevertheless, meaningfulness of such analyses has seldom been questioned. Reliable measuring of non-financial entities by monetary units is by definition impossible and also unreasonable. In an economic evaluation, to override this absurdity, an approach is taken on the basis of assessing future productivity worth from being able to return to work or determining how much people are willing to pay for the improvement in health (Drummond et al. 1996).

Cost-effectiveness ratio, willingness to pay and value of life all are concepts mixing financial and non-financial issues. Even though economic evaluation provides essential information for decision-makers, measuring value of life or health by monetary terms also incorporates a risk of inhuman conclusions. As costs for treating a certain disease or certain patient are known, it is easy to calculate how much savings could be achieved by deciding not to treat those diseases or patients.

6.8.1 Valuing life

The value of life, if regarded rational, may be estimated by calculating the relative increase in salary required for a worker to incur an increase in occupational risk (Lee et al. 2006). For example, by utilizing mathematical annual risk of death 0.004 for an US contractor in Iraq and salaries ranging from (US\$) 60 000 to 175 000 compared with a salary of 30 000 per year over comparable occupations in the United States, contractors are compensated at a rate of 250 000 per statistical year of life (Lee et al. 2006). Whether the decision to enlist for a contractor in Iraq is preceded by a proper forethought of risks and advantages and, conclusively, whether figures based on such an analysis really reflect the value of life, must be questioned. Values counted on the basis of occupational risks are considerably different when a worldwide perspective is taken. Compared with US contractors, many workers in underdeveloped countries must take much more noticeable risks with much lower compensation rates.

Another issue affecting the monetary value of life is how concrete the risk of death really is. A moderately increased relative occupational risk may be regarded insignificant and the amount of required extra compensation is modest. To the contrary, the subjects who are in immediate danger knowing that they are about to die soon, are probably prone to pay anything to stay alive. For obvious reasons, randomized controlled economic studies assessing the value of life from this perspective have not been conducted so far. In practice, maybe the most common examples of a concrete valuing of life are those individuals who decide to forego their lives for ideological or religious reasons. In those cases, life is regarded as a tradable object indeed and, for instance, present life is traded with a martyr death and an eternal life beside still waters. Whether these choices are constituted on evidence-based economic facts remains unanswered. Approaches evaluating effectiveness of life-saving interventions in non-medical fields such as programs improving transportation safety, occupational health or environmental hazard control have also been applied (Lee et al. 2009).

6.8.2 Measuring outcomes in health care

Commonly used hard end-points such as survival, vascular events and a need for hospitalization are usually obvious and reasonably easy to measure in clinical trials. However, taking a wider perspective will result in a more complex setting. When the state of health is assessed as a whole instead of single events, determining the benefit or effectiveness is not a straightforward matter and several decisions can markedly affect the results: Which factors are included in the analysis and how they are evaluated? What is the time horizon? Are there side effects which have an effect on the outcomes? Generalizability of results may be limited and benefits observed in a clinical trial cannot necessarily be extrapolated to the rest of the population.

Recommendations concerning best research methods have suggested including the practice of sensitivity analyses (Drummond et al. 1996; Siegel et al. 1996). In health economic evaluation, the impacts of certain factors may be difficult to measure. Sensitivity analyses can be used to examine the degree of uncertainty and they assess how study results would change if parameters, such as effectiveness, were measured differently and instead of one result, a range of potential outcomes is provided.

6.8.3 Measuring quality of life

Several different methods are applied to assess quality of life and there is no consensus on the best technique for determining patient well-being. Studies evaluating HRQOL in dialysis patients have reported somewhat conflicting results (Griva et al. 2013), possibly due to differences in patient populations and selection policies. However, differences between methods may also affect the results. Hornberger et al reported substantial variability among commonly utilized questionnaires. 58 dialysis patients were interviewed and their HRQOL were determined by using six different methods. Correlation coefficients between the methods were poor (range 0,094–0,519) and discrepancies were particularly apparent as data were evaluated at the individual level. The authors conclude that, depending on the technique chosen to evaluate HRQOL, patients with similar diseases and treatment regimens may report varying estimates of their well-being. Reported HRQOL directly affects cost-utility and CUAs utilizing a single estimate of HRQOL are prone to bias. To avoid bias, the authors suggested considering to apply an array of HRQOL measures. (Hornberger et al. 1992)

As the variability among methods to assess HRQOL is acknowledged, their overall eligibility in grading life among individual patients may also be argued. Reducing a multi-dimensional entity such as quality-of-life into a single figure produces averaged and simplified outcomes. Can we assume that HRQOL 0,6 in a diabetic PD patient with severe coronary artery disease is equal with HRQOL 0,6 in a HD patient with visual impairment and mental depression? And, if one should make the choice in the real life instead of hypothetical possibilities, would three years of life in a health state 0,3 and one year of life in 0,9 be tradable and equivalent options for that particular subject? On the other hand, describing and measuring complex issues as simple numbers is common in the whole field of medical research and no better instruments have been developed so far. By utilizing HRQOL in economic evaluation, at least some distortion may be avoided when various treatments with remarkably different outcomes are compared with each other.

6.8.4 Interpreting cost-effectiveness ratios

Making decisions based solely on individual CERs (like cost/QALY) is hazardous and incorporates a risk of perverse conclusions. This is illustrated in Table 13. Costs in hypothetical Therapy 1 are, say, EUR 5000 and the average number of

life-years gained is 0,5. In this treatment, HRQOL is relatively poor and cost/QALY is mathematically EUR 20 000 – after that none of the patients actually survived up to one year. Compared with Therapy 1, more costs are produced by Therapy 2 but patients’ quality of life is perfect and the mean survival is three years. Cost/QALY (CER) in Therapy 2 is also EUR 20 000, identical to the CER in Therapy 1. In Therapy 3, EUR 100 000 costs are incurred and 10 life-years are achieved but patients’ HRQOL is severely impaired resulting in cost/QALY EUR 20 000, again. From a clinical perspective the three therapies are remarkably different even though similar CERs are presented.

In comparing between two options, utilizing ICER instead of individual CERs measures both changes in costs and outcomes. In therapy 2, compared with Therapy 1, an additional 55 000 charge is needed to achieve 2,75 QALYs. An ICER 20 000/QALY is thus produced and Therapy 2 can be judged to be cost-effective compared with Therapy 1. Instead, in Therapy 4, with a similar cost/QALY, outcome (number of QALYs) is poorer than in Therapy 1. While Therapy 4 does not result in an improvement in health, it neither is cost-effective.

Table 13. Hypothetical treatment options with different costs and outcomes

	Cost	Life-years gained	Quality of life	QALYs	Cost/QALY
Therapy 1	5 000	0,5	0,5	0,25	20 000
Therapy 2	60 000	3	1	3	20 000
Therapy 3	100 000	10	0,2	5	20 000
Therapy 4	4 000	0,5	0,4	0,2	20 000

Effectiveness is usually reported as the mean of gained life-years. However, the distribution of subjects' survival may be markedly different from the normal distribution. In that case, the use of the average figure to calculate CER insufficiently demonstrates outcomes, as illustrated in Table 14. Of four patients in Therapy 5, three survived for six months and one patient for 6,5 years, whereas in Therapy 6 all patients stayed alive for two years, exactly. In both therapies, the average number of gained life-years were 2,0. If the purpose of the analysis is to determine the CERs for individual years – as it frequently is when RRTs are evaluated – the percentage of patients actually surviving and completing the particular year has to be taken into account.

Table 14. Hypothetical treatment options with different distribution of survival

	Cost	Life-years gained (mean)	One-year survival	Quality of life	QALY	Cost/QALY
Therapy 5	40 000	2,0	25%	1	2	20 000
Therapy 6	40 000	2,0	100%	1	2	20 000

6.8.5 Willingness to pay

Maximum acceptable ICER – willingness to pay for a particular treatment – depends on context and establishing one universal figure cannot be attained. Severity of illness, amount of achievable health gain, patient characteristics and society's economic status all contribute to the decision. Undoubtedly, magnitude of the problem also plays a role when limits are determined. ESRD patients account for approximately 0,08% of population in Finland and their entitlement for RRT is self-evident. If we considered a hypothetical new treatment which lengthens life in all citizens by a cost attributable to costs in RRT – for example EUR 50 000 in a year – the amount of money needed would approximate EUR 250 billion which exceeds the gross domestic product in Finland (EUR 193 billion in 2013) (http://www.tilastokeskus.fi/tup/suoluk/suoluk_kansantalous.html).

The role of dialysis therapy in determining the societies' valuation for a statistical year of life is unique and crucial. In 1972 the United States government decided to entitle patients with ESRD to reimbursement of RRT within Medicare program. So far it has remained the only example where Medicare coverage is universal and granted solely on the basis of a diagnosis. This has tempted researchers in the medical field to add normative judgment to comparisons between various treatments: society ought to reimburse for other treatments with at least similar cost-effectiveness compared with dialysis therapies (Winkelmayer et al. 2002). Thus, health economic decisions for acceptance of other medical interventions can be made relative to dialysis and the cost of dialysis therapy is broadly quoted as a benchmark for the willingness to pay -threshold of medical technologies (Lee et al. 2009). Based on data from a Canadian study in 1984 including 44 dialysis patients and prices related Canadian \$ in 1980, the number of US\$ 50 000 has frequently been applied as the cost of dialysis per QALY (Churchill et al. 1984; Winkelmayer et al. 2002). Recent studies have shown that this sum has increased beyond inflation, possibly due to innovations in nephrology and dialysis care and liberal acceptance of older and sicker patients in dialysis therapy. Instead of US\$ 50 000, authors in recent literature have suggested that figures from US\$ 93 500 to 129 090 per QALY were more accurate (Eichler et al. 2004; Lee et al. 2006).

6.8.6 Discounting

While the flow in expenses is continuous both in HD and in PD and no particular starting investments are necessitated (regardless of costs for arteriovenous fistula or peritoneal catheter, which are of minor importance), the question whether to discount or not to discount is not essential in economic comparison between dialysis modalities. For that reason, discounting was not applied in cost-effectiveness analysis in Study II. However, if there was an intention to design a cost-effectiveness analysis comparing between dialysis therapies and TX, discounting would be necessary to avoid bias caused by high first-line costs for transplantation procedure. Discounting is recommended in studies having a long time horizon. Especially in interventions with high initial costs the selected discounting policy markedly contributes CER. In dialysis therapies there is an ongoing need to offer treatment to the patients to keep them alive and the amount of required costs remains rather stable in individual years.

6.8.7 Perspective and time horizon

It is important to recognize the perspective from which a CEA was conducted. Usually, outcomes are straightforward to measure and they are not affected by the choice of perspective. To the contrary, costs may markedly vary and different viewpoints provide different results.

When taking a payer's perspective, costs are measured as charges which depend on accounting methods. Reimbursement rates, determined by funding authorities, may not reflect real production costs, but they are supposed to at least cover the costs (De Vecchi et al. 1999). Patient copayments and value of informal caregiver's time are not accounted for. From a provider's perspective – which was applied in Studies I–IV – absolute production costs of a certain treatment or technology can be determined and they may substantially differ from its fixed amount of reimbursement. In public systems, absence of market prices and competing treatment providers may distort pricing. In many cases expenditures are divided across several budgets. Due to fragmentation, the full impact of certain interventions is difficult to assess. For example, introduction of a new drug may increase costs for medication but, if concomitant need for hospitalization decreases, the net effect may be cost-saving. Conclusions made by decision-makers may be opposite depending on the available information.

In Studies I–III costing method determined both a detailed use of health care services and overhead costs and individual cost factors were recorded minutely. Costing procedures vary across countries and therapies comprise a different blend of services and products (Karopadi et al. 2013). Studies reporting costs for dialysis may limit the scope to the dialysis treatment only thus ignoring cost arising from essential medications, hospitalizations and comorbidities. Assessing only treatment-related costs and ignoring other costs which possibly are indirectly influenced by the treatment, is simple but may cause bias to results. In the United States the common practice (for financial reimbursement reasons) in register studies is to define the 90th day after starting RRT as day 0 (Collins et al. 2013). Those patients who die within the first 90 days are excluded from the analysis. Including the lucky survivors and ignoring non-survivors incorporates a potential risk of bias.

Macroeconomic factors also contribute to outcomes. In Western Europe and North America there has been – so far – almost unlimited acceptance to RRT whenever it is medically indicated and funding of the treatment is arranged by governments or social insurance programs. In developing countries the situation is markedly different. Societies' subvention for treatment costs does not exist and

payments for RRT – if available – are borne by patients' out of pockets expenses. For instance in Nigeria, the costs for a single HD session and a CAPD day were recently estimated at about US\$ 130 and US\$ 80, respectively. Only 6,8% of patients could afford the treatment for longer than three months. Subsequently, survival of patients was extremely poor and median survival after diagnosis of ESRD was only two weeks (Arogundade et al. 2011). Self-evidently, results of health economic studies must be interpreted in the context of their socioeconomic background.

Cost-effectiveness of an intervention with higher up-front costs but lower long-term costs compared with another (for instance kidney transplant compared with hemodialysis) depends on follow-up. If only the first year is considered, kidney transplant seems not to be an attractive option, but when taking 10 years follow-up, the conclusion is opposite. Generally, guidelines recommend employing a lifetime horizon (Erickson et al. 2010).

Economic studies have been written both from the payers' and providers' perspectives and they have been conducted in a variety of developed and developing countries, with various assumptions and funding regimes. Unique characteristics in individual studies limit the generalizability of results (Komenda et al. 2012). It has been suggested to apply a societal perspective in order to consider all relevant costs and to avoid biases that may be incorporated in a narrower approach (Russell et al. 1996). On the other hand, absolute accuracy in determining costs or benefits of a certain intervention is impossible to achieve. Costs arising from losses of productivity, decreased tax payments or early retirement can only be estimated.

7 SUMMARY AND CONCLUSIONS

The main findings of the present study are summarized as follows:

1. In patients eligible for PD, treatment costs may be slightly lower than costs on HD: Costs were somewhat lower in patients selected primarily to PD compared with costs in HD patients. Treatment costs in HD patients were 8–27% higher than they were in PD patients and differences between the groups were largely attributable to differences in the cost for transport and, to a lesser extent, to higher costs for medication in HD patients. In both modalities, approximately half of the total expenditures were caused by the dialysis therapy itself. Costs for hospitalization and medication were the second and third largest items. Together, costs for dialysis therapy, hospitalization and medication explained 79–88% of total costs.
2. The high initial costs for TX are balanced during the following months, after which TX induces considerably less costs than dialysis therapies: Due to high costs of the transplantation procedure and subsequent close monitoring, costs (US\$) for the months 0–6 were higher (38 265) in TX patients compared with patients in HD and PD (32 566 and 25 504, respectively). After that, costs lowered markedly in TX patients whereas they were rather stable in HD and PD. Annual costs in TX recipients in years 2 and 3 were in between 9240–11 446 comprising only 17–31% of costs in dialysis therapies. Of costs in TX patients, expenses for medication were the largest item causing 59–67% of total costs and rest of costs were divided rather evenly between hospitalization, outpatient control visits, laboratory tests and transport.
3. Compared with HD, PD may be a cost-effective treatment in eligible patients: Cost-effectiveness of dialysis therapies were evaluated by determining four alternative cut-points of follow-up. PD was found to dominate over HD in three strategies (intention-to-treat, time on dialysis and time on primary modality). When considering technique failure as death (death of modality -approach), more life-years were gained with HD but the ICER was over 444 000 US\$/QALY. Results of a subanalysis including 68 matched HD–PD patient pairs were comparable with the whole population. CERS for three years varied from some 313 000 to 471 000 in HD and from 200 000 to 320 000 in PD.
4. Achieving targeted PTH levels may be associated with lower costs in dialysis patients and a positive correlation between CRP and costs and an inverse correlation between albumin and costs were found: In patients with constantly low

PTH (below K/DOQI target), the average daily costs (US\$) were statistically significantly higher than in patients with at least one measurement between targeted limits (170 vs. 148, respectively). In subjects with PTH constantly over target costs were 172, statistically significant difference compared with the in-target group was not reached. In patients with near-optimal (as was defined in K/DOQI recommendations) mineral metabolism levels the average daily costs were 145 compared with 165 in subjects with non-optimal levels. The difference was statistically insignificant. Statistically significant positive correlation was found between costs and CRP whereas costs and albumin were inversely correlated.

5. An outpatient PDCI is safe and it causes less cost than an inpatient PDCI: No difference in rate of complications or outcomes was found when results of inpatient and outpatient PDCIs were evaluated. Twenty-two percent of patients experienced a catheter-related complication within 30 days after the procedure. The incidence rates of technique failure and peritonitis were 1 per 41 months per patient and 1 per 18 months per patient, respectively. Overall one-year catheter survival was 72%. Total average costs of the PDCI were statistically significantly lower in outpatients (EUR 1346) compared with inpatients (EUR 2320).

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Cost Analysis of Renal Replacement Therapies in Finland

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● **Background:** Costs for treating patients with end-stage renal disease (ESRD) have grown noticeably. However, most of the cost estimates to date have taken the perspective of the payers. Hence, direct costs of treating ESRD are not accurately known. **Methods:** Files of all adult patients with ESRD who entered dialysis therapy between January 1, 1991, and December 31, 1996, were studied retrospectively, and all use of health care resources and services was recorded. Follow-up continued until December 31, 1996. **Results:** Two hundred fourteen patients fulfilled the study criteria, 138 patients started with in-center hemodialysis (HD) therapy, and 76 patients started with continuous ambulatory peritoneal dialysis (CAPD) therapy. Patients were followed up until death (72 patients) or treatment modality changed for more than 1 month. Fifty-five patients received a cadaveric transplant, and after transplantation (TX), they were examined as a separate group of TX patients. Direct health care costs for the first 6 months in the HD, CAPD, and TX groups were US \$32,566, \$25,504, and \$38,265, and for the next 6 months, \$26,272, \$24,218, and \$7,420, respectively. During subsequent years, annual costs were US \$54,140 and \$54,490 in the HD group, \$45,262 and \$49,299 in the CAPD group, and \$11,446 and \$9,989 in the TX group. Regression analyses showed 4 variables significantly associated with greater daily costs in dialysis patients: age, ischemic heart disease, nonprimary renal disease, and HD treatment. **Conclusion:** Compared with HD, CAPD may be associated with lower costs, yet the absolute difference is not striking. After the TX procedure is performed once, annual costs decline remarkably, and cadaveric TX is less costly than both dialysis modalities. *Am J Kidney Dis* 42:1228-1238.

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INDEX WORDS: Continuous ambulatory peritoneal dialysis (CAPD); cost; end-stage renal disease (ESRD); hemodialysis (HD); kidney transplantation (TX).

COSTS FOR MEDICAL care are increasing rapidly, and especially end-stage renal disease (ESRD) expenditures have grown remarkably. Renal transplantation (TX) has been shown to be more cost-effective than dialysis therapy,¹⁻⁷ and it also is believed to provide a considerable improvement in health-related quality of life,⁸⁻¹¹ whereas comparisons between in-center hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) therapy have given, to some extent, contradictory results. According to some investigators, CAPD is less costly than in-center HD,¹²⁻¹⁵ whereas some investigators have not found significant differences between these modalities.^{14,16} In a Brazilian study, HD treatment was associated with greater costs, but a better cost-effectiveness ratio, than CAPD.⁶

Results of reported studies still have some

limitations. In many studies, costs are measured as reimbursements by health insurance to dialysis centers, which does not reflect actual production costs.¹⁷ Some subgroups (patients with diabetes and those with cardiovascular diseases) have been excluded,⁶ as have costs of outpatient prescription medication.¹² Precise costs of ESRD treatment have not been calculated. Many of the key parameters required for dealing accurately with such a topic are either missing or inadequately estimated in the sources of information.¹⁸ Here, we performed a detailed analysis of direct health care costs of the most used renal replacement therapies (RRTs) in Finland; namely, in-center HD, CAPD, and cadaveric TX.

PATIENTS AND METHODS

Patients and Follow-Up

Patients were recruited from the Department of Medicine at Tampere University Hospital (TaUH; Tampere, Finland; region population, ~440,000). All adult patients with ESRD scheduled for RRT between January 1, 1991, and December 31, 1996, were included in this study, either through outpatient follow-up or when RRT was started as an emergency procedure. Their files were studied retrospectively by one of us (T.S.). Additional data from local hospitals and health centers were collected, as well. Follow-up started on the day dialysis was first performed and continued until the end of 1996, death, or loss to follow-up because of transfer to another district or renal function recovery. The predialysis period was not assessed. Patients who had undergone RRT

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Table 1. Breakdown of Costs of a Single HD Session and a 1-Day Hospitalization at TaUH

	HD Session	General Ward	Cardiac Care Unit	Intensive Care Unit
Salaries (US \$)	101	111	283	937
Material, supplies (US \$)	65	21	73	424
Administration, maintenance, amortization, miscellaneous (US \$)	27	94	111	284
Total (US \$)	193*	226	467	1,645

*Intradialytic medications cost an additional \$81/session/patient, and laboratory, radiological, and other analysis related to HD session, \$24, respectively. Data from the hospital accounting system.

previously and restarted it during the study period were excluded. Diagnostic classification was based on the cause of ESRD obtained from the files.

Modality Definition

The RRT mode adopted was based on the patient's choice, his or her medical status, and the current availability of HD facilities. Assignment of treatment modality was performed on an intention-to-treat basis: Patients starting with HD therapy belonged to the HD group, and patients were classified as CAPD patients if it was the modality primary initiated. Sometimes RRT was obliged to start acutely with HD, but if this period was shorter than 30 days and CAPD was the modality planned in predialysis time, these patients were still regarded as CAPD patients. Patients who received a cadaveric transplant during the study period were considered as having started a new life track and were examined as a separate modality group.

Costing Procedures

Cost analysis took the perspective of service providers, and the costing method determines direct health care costs associated with each treatment, including overhead costs caused by infrastructure, administration, amortization, and so on.

All resource use was valued at prices in 1997. All costs were converted to US dollars using an exchange rate of US \$1 equal to 5.1944 Finnish marks.

HD Session

Patients normally underwent 3 weekly treatments of 4 hours. For all patients, HD therapy was started at TaUH, but after a stable period, therapy was continued as satellite dialysis for 25 patients living far from TaUH. The number of weekly HD sessions during follow-up per patient was recorded. A Cimino-Brescia-type arteriovenous (AV) fistula usually was used for vascular access. If this was not possible, a central venous HD catheter was inserted. The cost for a single session, excluding costs of laboratory and radiology tests and intradialytic and interdialytic drugs, was US \$193. A detailed analysis of costs is listed in Table 1.

A CAPD Day

Patients performed CAPD at home and visited the dialysis unit once a month for an outpatient check-up. A Tenckhoff

catheter (implanted by surgical dissection in the operating room) was used for peritoneal access. Dialysis fluids used were Dianeal (Baxter BV, Utrecht, The Netherlands) and Lockolys-Glucos (Fresenius AG, Bad Homburg, Germany), and these 2 products were used practically equally (52.1% and 47.9% of peritoneal dialysis [PD] days, respectively). The dialysis schedule most often followed was 4 daily bag exchanges (84.1% of PD days). Patients on CAPD training were mostly in inpatient care. Intermittent PD was performed only at the beginning of dialysis therapy (average length, 13.5 days; maximum, 30 days) and is classified as a form of CAPD training in this study. Continuous cycling PD accounted for only 4.2% of total PD days, was used by 4 patients, and is analyzed as CAPD.

Daily CAPD costs, including fluids, hoses, protective caps, disinfectants, and other equipment, were assessed to be US \$58 to \$96, depending on fluid volume and number of bag exchanges. The most often used forms (4 exchanges, 2-L volume) cost US \$77 (Dianeal) and \$75 (Lockolys-Glucos), respectively. Dialysis costs on CAPD include solely costs for fluids and equipments, and costs arising from other resources and services (eg, hospitalization, medication) were added as separate categories.

Cadaveric TX

Renal TX in Finland is performed in a centralized manner at Helsinki University Hospital. All transplants among the study population were cadaveric. The cost of the TX procedure was US \$5,150, and the average cost for a 1-day hospitalization, including medications, laboratory and radiological analyses, and possible dialysis therapy, was \$756 in 1996. The stay in Helsinki University Hospital typically was approximately 3 weeks. After TX, all patients received standard immunosuppressive therapy: a combination of azathioprine, methylprednisolone, and cyclosporine.

Hospitalizations

The daily cost of hospitalization at the general ward in the Department of Internal Medicine was US \$226 (detailed analysis listed in Table 1). This figure contains only "hotel" costs (eg, capital costs, maintenance services, meals, plumbing, and employee salaries), but not costs for examinations or medicines. Daily costs at the Intensive Care Unit and Cardiac Care Unit were US \$1,645 and \$467, respectively (Table 1). Hospitalizations at departments of TaUH other

than the Department of Medicine were rare, and hotel costs did not differ among departments. Local hospitals and health centers were asked to produce their hospitalization costs, and these numbers were used directly. Eighty percent of all hospital days took place at TaUH.

Medications

Patients' medications during the study period were recorded in detail. This includes such medicines during the dialysis sessions as erythropoietin (EPO), intravenous antibiotics, and liquids during hospitalizations and outpatient prescription medications.

Consultations and Outpatient Checkups

Visits to different outpatient clinics at TaUH were recorded, and data for costs of single visits were obtained from the hospital accounting system. These costs do not include laboratory or other examinations. Visits to local hospitals and health centers were registered, as well.

Transportation

Patients were living in an area with a diameter of 115 km (average, 27 km). They principally used a taxi for regular HD visits and CAPD controls; thus, transportation costs were calculated solely on the basis of taxi costs (US \$0.96 for 1 km).

Invasive Examinations, Surgical Procedures, and Central Venous Punctures

Costs for AV fistula procedures and peritoneal catheter implantation before the initiation of dialysis therapy also were included in the analysis and were added to patient costs for the first 6 months. The number and dates of all surgical procedures and invasive examinations were recorded. Implantations of central venous catheters by anesthesiologists also were registered. Numbers and costs of the most costly events are listed in Table 2.

Other Costs

Detailed data for costs of laboratory tests performed during the study period of all patients were obtained from the database of the Central Laboratory of TaUH. Costs of laboratory tests performed elsewhere than TaUH were not calculated, although they were estimated to be very low and of no importance.

Examinations performed at the Departments of Radiology, Clinical Physiology, Neurophysiology, Nuclear Medicine, and Pathology were identified, and cost data for these examinations were obtained from the respective units.

Calculation of Mean Costs

Mean costs in different treatment modalities were obtained by dividing RRT costs in separate treatment modalities for a given period by the respective number of observed days in a given period multiplied by the length of the period. In this analysis, patients in the HD and CAPD groups were followed up until death or treatment modality changed for more than 1 month. Follow-ups of HD and CAPD patients receiving a cadaveric transplant were censored at the time

Table 2. Numbers and Costs of the Most Cost-Producing Surgical Procedures, Invasive Examinations, and Central Venous Catheter Implantation

	No. of Patients	Cost/ Intervention (US \$)
AV fistula construction	309	1,348
Central venous catheter implantation	179	90
Peritoneal catheter implantation	105	1,348
Peritoneal catheter removal	52	674
Coronary angiographies	26	1,110
Cataract extraction	21	760
Below-the-knee amputation	14	1,348
Vitrectomy	10	2,329
AV vascular prosthesis	9	1,925
Endoscopic cholecystectomy	9	1,444

the TX procedure was performed, and they started a new life track as TX patients.

Statistical Analysis

Patient characteristics were compared between the HD and CAPD groups by means of Student's *t*-test for continuous variables and Spearman's chi-square test for categorical variables. Overall patient survival was estimated using the Kaplan-Meier method. When considering survival of all patients, survival is defined by death, censoring in the end of the study period, or when a living patient withdrew for other reasons. Survival among modalities was compared by using log-rank test. When survival was considered in different treatment modalities, survival is defined by death, censoring in the end of the study period, or when a living patient withdrew for other reasons or underwent TX (for HD and CAPD patients). Transplant recipients started a new life track as TX patients. Stepwise multiple regression was performed to identify factors associated with daily costs and survival. Calculations were performed using SPSS for Windows, version 6.1.3 (SPSS Inc, Chicago, IL; 1989 to 1995).

RESULTS

Two hundred fourteen patients (120 men, 94 women) fulfilled the study criteria. Patient age at onset of dialysis therapy ranged from 15 to 84 years; mean age was 56.5 ± 1.0 (SEM) years. Mean age of men was slightly younger than that of women (54.8 ± 1.3 versus 58.8 ± 1.6 years; $P = 0.028$). Diagnostic groupings are listed in Table 3. The group with diabetic nephropathy was the largest, with 76 patients (35.5%); 33

Table 3. Patient Diagnostic Grouping, Age, and Sex

Diagnostic Group	Patients	Men	<50 y	No. of Renal Biopsies (% of total group)
Primary renal diseases	86 (40.2)	54 (62.8)	30 (34.9)	53 (61.6)
Chronic glomerulonephritis	54 (25.2)	37 (68.5)	21 (38.9)	51 (94.4)
Interstitial nephritis	20 (9.3)	11 (55.0)	7 (35.0)	2 (10.0)
Polycystic kidney disease	12 (5.6)	6 (50.0)	2 (16.7)	0 (0)
Nonprimary renal diseases	128 (59.8)	66 (51.6)	38 (29.7)	19 (14.8)
Diabetes	76 (35.5)	42 (55.3)	29 (38.2)	9 (11.8)
Amyloidosis	20 (9.3)	8 (40.0)	7 (35.0)	4 (20.0)
Miscellaneous nephropathies	32 (15.0)	16 (50.0)	2 (6.3)	6 (18.8)
Total	214 (100)	120 (56.1)	68 (31.7)	72 (33.6)

NOTE. Values expressed as number (percent).

patients had insulin-dependent diabetes mellitus and 43 patients had non-insulin-dependent diabetes mellitus. The group with chronic glomerulonephritis included 54 patients (25.2%). The amyloidosis group consisted of 19 patients with secondary amyloidosis and 1 patient with primary amyloidosis. Interstitial nephritis was found in 20 patients. The group with miscellaneous nephropathies consisted of 32 patients (15.0%) with undefined chronic nephropathies and secondary nephropathies other than diabetic nephropathy and amyloidosis; 15 of these patients had hypertensive nephrosclerosis.

There were 138 HD patients and 76 CAPD patients in this study. Mean follow-ups were on average 23 months in the HD group and 28 months in the CAPD group. Demographic data for different treatment modalities are listed in Table 4. Patients used multiple treatment modalities over time. Twenty-seven patients (36%) had to change from CAPD to HD therapy because of technical failure, usually recurrent peritonitis epi-

sodes (Table 5). Nineteen treatment failures occurred during the first year. The combined rate of peritonitis and catheter infection was 0.68 episodes/patient/y, and the catheter implantation rate was 1.12 catheters/patient/y. Twelve patients changed voluntarily from HD to CAPD therapy, none of them because of technical failure.

Cadaveric TX was performed on 55 patients (26% of the study population); hence, the average annual TX rate was 21 TX/million population. Mean age of transplant recipients was 45.0 years (range, 16 to 65 years; Table 4). Of all transplant recipients, 48 patients (87%) maintained sufficient renal function, 4 patients returned to dialysis treatment because of graft failure, and 3 patients died by the end of the study period. No patient underwent re-TX during the study period. Average time on dialysis therapy before TX was 14.4 months for all transplant recipients.

Patient Survival

During the study period, 72 patients (34%) died and 8 patients were withdrawn because of transfer to another district or renal function recovery. Death rates in each treatment modality are listed in Table 4. Higher mortality in HD patients explains the shorter follow-up of the HD group. Mortality in patients aged 15 to 39 years was 11%; in those aged 40 to 54 years, 28%; and in those older than 55 years, 42%. Cardiovascular diseases caused more than half the deaths, and infections, approximately one sixth of deaths. Median survival time for all patients was 57.7 months (Fig 1). Patients on CAPD therapy seem

Table 4. Demographic Data

	No. of Patients	Mean Age (y)	Deaths	TX
HD	138	58.6 ± 1.2	56 (41)	29 (21)
CAPD	76	51.1 ± 1.9	16 (21)	26 (34)
<i>P</i> (HD v CAPD)		0.000	0.006	0.051
All	214	56.5 ± 1.0	72 (34)	55 (26)
TX*	55*	45.0 ± 1.6	3 (5)	

NOTE. Values expressed as mean ± SEM or number (percent).

*TX group consisted of 29 patients starting on HD therapy and 26 patients starting on CAPD therapy.

Table 5. Patient Outcomes During Consecutive Yearly Observations

Year	No. of Patients Starting the Examined Year	Change to CAPD or HD	Death	TX	End of Follow-Up	Still on First Modality at End of Year
HD						
1	138	12 (9)	29 (21)	12 (9)	24 (17)	61 (44)
2	61	0	13 (21)	9 (15)	8 (13)	31 (51)
3	31	0	5 (16)	2 (6)	8 (26)	16 (52)
4	16	0	2(13)	1(6)	6(38)	7(44)
CAPD						
1	76	19 (25)	2 (3)	12 (16)	16 (21)	27 (36)
2	27	4 (15)	3 (11)	5 (19)	3 (11)	12 (44)
3	12	3 (25)	1 (8)	2 (17)	2 (17)	4 (33)
4	4	1 (25)	0 (0)	0 (0)	2 (50)	1 (25)

NOTE. Values expressed as number (percent).

to survive significantly better than patients on HD therapy ($P = 0.0025$), but if technical survival is considered, there was no significant difference in survival between the HD and CAPD groups ($P = 0.58$).

Cost Analysis

Mean costs in different treatment modalities. Mean costs in the different groups and periods are listed in Table 6, and cost breakdown is shown in Fig 2. Costs for the first 6 months were greatest among TX patients at US \$38,265, and

for HD and CAPD patients, costs were \$32,566 and \$25,504, respectively. Costs in the TX group declined abruptly during subsequent periods, but were stable in patients treated with HD and CAPD. During the 3 years of follow-up, costs remained at approximately the same level and differences were negligible. There was no significant difference in costs between men and women (Tables 7 to 9). Treatment of patients with nonprimary renal disease caused slightly greater costs than treatment of patients with primary renal disease. Also, CAPD costs of patients with diabe-

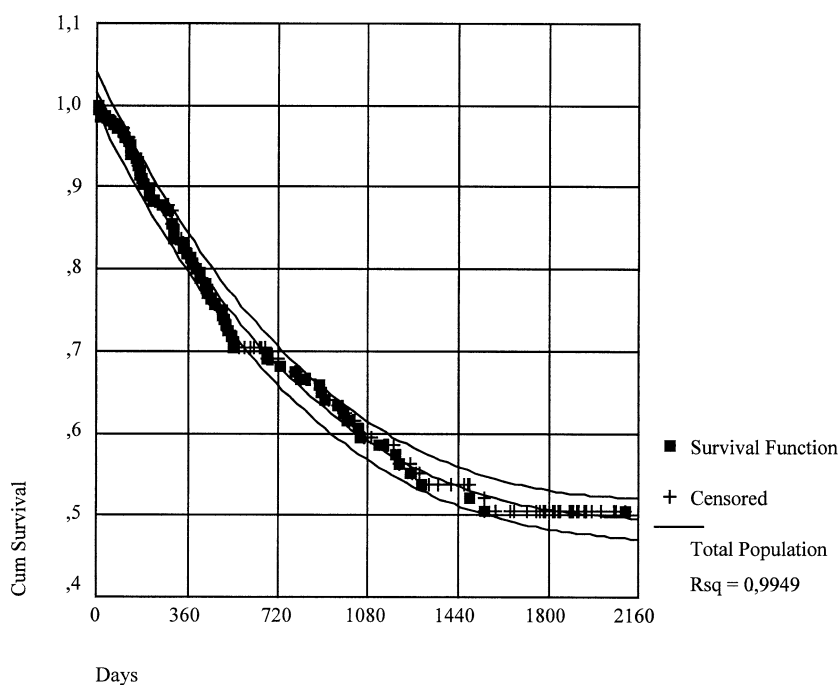


Fig 1. Patient survival by Kaplan-Meier method with cubic regression line with 95% confidence intervals.

Table 6. Mean Costs in Different Treatment Modalities

		Months 1-6	Months 7-12	Year 2	Year 3
HD (US \$)	Mean	32,566	26,272	54,140	54,490
	SEM	1,093	1,149	3,459	3,650
	No. of patients	138	95	61	31
CAPD (US \$)	Mean	25,504	242,18	45,262	49,299
	SEM	1,094	1,685	3,338	2,963
	No. of patients	76	53	27	12
TX (US \$)	Mean	38,265	7,420	11,446	9,240
	SEM	2,043	669	1,316	464
	No. of patients	55	49	43	33

tes and those older than 50 years were greater, but for HD patients, there was no such trend.

Multiple regression model. Four variables turned out to be statistically significant in explaining the variance in daily costs: age, ischemic heart disease, primary renal disease, and treatment modality. Age increased daily costs by approximately US \$0.81 (\pm \$0.35) per year of age, and the presence of heart disease increased daily costs by \$34.7 (\pm \$14.2). Costs of treating a patient with ESRD with primary renal disease were US \$63.7 (\pm \$12.7) less per day than those for treating a patient with nonprimary renal dis-

ease. Modality group also had a noticeable effect on costs. According to this model, treating a patient with CAPD instead of HD saved US \$35.6 (\pm \$10.8) per day. However, the explanatory power of the model is not very high ($R^2 = 0.21373$), and SEs are large.

To examine the effects of separate underlying causes of ESRD, the covariates primary and nonprimary renal diseases were replaced by individual diagnoses. Interestingly, in this model, none of the examined diagnoses had a statistically significant effect on costs. Treatment modality and presence of heart disease remained among

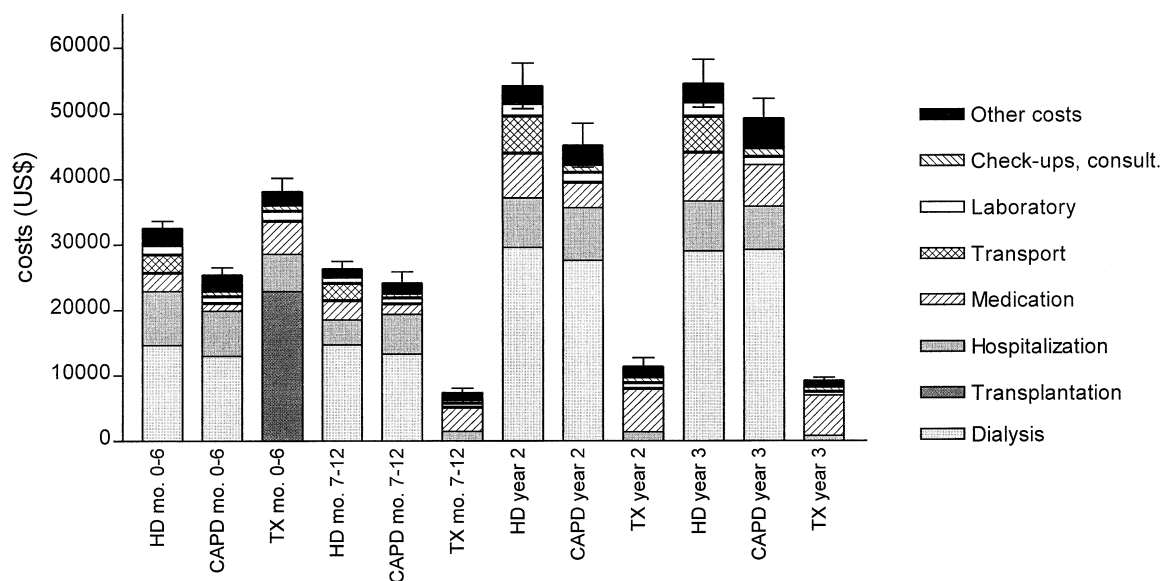


Fig 2. Mean costs in different treatment modalities. Dialysis, solely costs for HD sessions or CAPD fluids and equipment; Transplantation, cost of TX procedure; Hospitalization, hotel costs for inpatient care; Medication, costs for inpatient and outpatient medicines; Check-ups and consultations, visits to outpatient clinics; Other costs, minor cost categories of operations, eg, radiological examinations, CAPD and TX patient transportation, HD patient consultations. Overhead costs are included in each category.

Table 7. Mean Costs for HD in Different Subgroups

Group	No. of Patients	Months 0-6 (US \$)	No. of Patients	Months 7-12 (US \$)	No. of Patients	Year 2 (US \$)
All	138	32,566	95	26,272	61	54,140
Men	80	32,717	52	27,080	34	59,309
Women	58	33,618	43	26,917	27	51,328
<50 y	29	31,531	19	29,707	9	75,448
50 y	109	33,538	76	26,459	52	52,876
PRD	54	29,298	42	23,999	24	52,554
Non-PRD	84	35,850	53	29,056	37	58,388
Diabetes	44	34,006	27	28,908	20	63,781
Nondiabetes	94	32,741	68	26,155	41	52,287

Abbreviation: PRD, primary renal disease.

the most cost-producing factors. Such variables as sex or body mass index did not have an effect on costs.

DISCUSSION

The retrospective file-based analysis makes it possible to accurately identify resources and services used that give rise to costs. Practically all possible cost data were obtained in this analysis except for costs of examinations and short-term transient in-patient medications in local hospitals and health centers. To our knowledge, this level of accuracy in recording cost factors in our study has not been achieved previously. Resources and services were valued at prevailing prices to the providers, instead of fee-scheduled reimbursements. Previous investigators mostly have taken the perspective of payers, and costs have been measured as reimbursements.^{2,6,14,16,19,20} The accounting methods are different between organizations, and contracts with suppliers are more or less favorable, contributing to profits achieved

by facilities. Taking the viewpoint of providers allows an accurate breakdown of expenses. Conversely, in this study, costs of the treatment of patients with ESRD were assessed as a whole instead of focusing on costs related directly to dialysis therapy or TX. Out of the scope of this study are costs arising in the social sector (eg, home help and staying in old people's home). However, it can be estimated that these costs are negligible compared with other costs. Of 86 patients on dialysis therapy at the end of 1996, only 9 patients used some of these services. Productivity costs (indirect costs) caused by early retirement and premature death were not considered in this study.

A third of the patients started their RRT with CAPD, and also at the end of the study period, the same proportion of dialysis patients were on CAPD therapy. This figure is very close to other countries with a publicly funded health care system, such as Sweden and Canada.^{21,22} Globally, 17% of patients with ESRD are undergo-

Table 8. Mean Costs for CAPD in Different Subgroups

Group	No. of Patients	Months 0-6 (US \$)	No. of Patients	Months 7-12 (US \$)	No. of Patients	Year 2 (US \$)
All	76	25,504	53	24,214	27	45,262
Men	40	24,318	26	21,487	16	43,463
Women	36	27,816	27	28,136	11	50,294
<50 y	40	23,940	31	20,943	17	39,662
50 y	36	27,742	22	27,328	10	49,137
PRD	32	22,292	23	21,272	12	45,653
Non-PRD	44	28,831	30	27,302	15	46,335
Diabetes	32	29,882	21	29,897	12	51,027
Nondiabetes	44	23,323	32	20,982	15	42,386

Abbreviation: PRD, primary renal disease.

Table 9. Mean Costs for TX in Different Subgroups

Group	No. of Patients	Months 0-6 (US \$)	No. of Patients	Months 7-12 (US \$)	No. of Patients	Year 2 (US \$)
All	55	38,265	49	7,420	43	11,446
Men	28	36,872	27	7,486	23	10,968
Women	27	40,327	22	7,648	20	12,456
<50 y	35	38,025	33	7,138	27	11,032
50 y	20	39,438	16	8,362	16	12,847
PRD	33	36,978	29	7,368	26	12,348
Non-PRD	22	40,785	20	7,849	17	10,560
Diabetes	14	37,299	14	8,497	11	10,802
Nondiabetes	41	38,946	35	7,216	32	11,972

Abbreviation: PRD, primary renal disease.

ing PD as the dialysis modality.²¹ Selection of a particular treatment modality, although not deterministic, is not completely random.⁴ Several factors, medical and nonmedical, affect selection, and no formal criteria have been followed.^{21,23} CAPD was the modality more likely offered if the patient had diabetes, was in moderate general condition, and not very aged. In the past, CAPD patients tended to be older and sicker than HD patients^{24,25}; however, recent studies have given figures similar to ours.^{4,12,14,16} Thus, patients on CAPD therapy were younger, uremia was caused more often by chronic glomerulonephritis or insulin-dependent diabetes mellitus, and the prevalence of cardiac disease was not as common as in patients on HD therapy. A remarkable proportion of CAPD patients did not succeed in their modality and were forced to switch modality, a problem well documented previously.^{13,24,26-28} Approximately 40% of CAPD patients who were followed up to 1 year and who did not receive a transplant had to change to HD therapy during the first year. Some of these patients returned to CAPD therapy later. During subsequent years, the shift from CAPD to HD therapy decreased markedly. Conversely, some HD patients transferred voluntarily to CAPD therapy. Hence, the proportion of dialysis patients treated with CAPD was continuously approximately 30%.

Several serious illnesses among patients with ESRD resulted in much greater mortality compared with the general population. In this study, the overall mortality rate was 33.6%, and most deaths occurred in the elderly and those who were primarily selected to HD therapy. Classification of patients according to the first treatment

modality gives much better survival to patients on CAPD than HD therapy. However, this kind of analysis does not take into account the switching among modalities and only shows that patients who will survive better are offered CAPD therapy as the first modality. When technical failure is considered as death, there is no difference in survival between modalities. A similar result was obtained in an Italian study.²⁸

Average direct costs for treating patients at TaUH are somewhat greater than at non-university central hospitals because of more teaching and scientific activities. The increase in costs for this reason is approximately 17% (data from the hospital accounting system; L. Kärki, personal communication, January 2000). The extra costs are not divided equally among modalities; they burden HD most because patients treated with HD have to visit the hospital more often than those treated with CAPD or TX.

Dialysis therapy itself was the most costly item in both dialysis therapies, accounting for approximately half the total expenditures in the HD group and more than half in the CAPD group. Annual costs were almost equal in both modalities (between US \$29,025 and \$29,553 for HD and \$27,570 and \$29,239 for CAPD). Costs for hospitalizations were the second largest item (after the first year, US \$7,593 to \$9,310 for HD and \$6,611 to \$8,090 for CAPD, respectively). Medication costs turned out to be somewhat greater for HD (US \$6,958 to \$8,756) than CAPD (\$3,974 to \$6,327), and there also was an increasing trend in medication costs during the study period, reflecting the growing role of EPO therapy: In 1991, only 6 of 26 dialysis patients were administered EPO; in 1996, EPO was ad-

ministered to 98 of 117 patients. There was a greater proportion of EPO users on HD than CAPD therapy each year, but the difference was statistically significant in 1992 only. EPO caused 38% of total medication costs. Transportation costs mainly burdened the HD group and were the most important cause of the slightly greater total expenses in the HD group. Despite the considerable number of laboratory tests, consultations, surgical procedures, and radiological and other examinations performed, their impact on total costs was only marginal. Total costs were at approximately the same levels reported in other studies; this applies also to the slightly lower expenses in CAPD patients.^{15,18,22,29}

Some investigators^{4,14,16,30,31} previously reported lower CAPD costs than in this study. Nonrenal outpatient physician consultations and oral medications were not included in 1 of these studies,¹⁴ and costs for transportation were excluded in another study.³¹ Compared with results of Bruns et al,³⁰ dialysis costs of CAPD in our study seem to be greater, possibly because of more expensive equipment. Also, costs for hospitalization in CAPD patients were high in our study, and there was no difference in hospitalization costs between HD and CAPD patients.

Direct costs for cadaveric TX were approximately US \$22,900/patient. After the TX procedure was performed once, annual total costs were only US \$9,240 to \$11,446, which is considerably less than costs for either HD or CAPD. Medications accounted for approximately 60% of total costs, and the exact amounts (US \$6,161 to \$6,741) were almost identical to medication expenses of dialysis patients. A Canadian study reported similar costs in the first year after TX; however, second-year costs were almost double compared with our results.³

When comparing daily costs, we used a multiple regression model to adjust for comorbidities, age, and other covariates; however, the explanatory power of the model did not meet our expectations. Ischemic heart disease turned out to be a very important variable affecting costs according to the regression model. Interestingly, patient age did not have a very significant effect on costs; it increased daily costs by only US \$0.81 per 1 year of age, and surprisingly, diabetes was a statistically insignificant variable in explaining the variance of daily costs.

Our model suggests that CAPD saves \$35.6 per day compared with HD, which is a remarkable amount, and it is difficult to give credence to being caused solely by the modality. Creating a well-designed model to explain costs in patients with ESRD is difficult. In a retrospective setting, controlling for all variables is inconvenient, and even after adjusting, there are still a lot of confounding factors favoring CAPD therapy. Compared with the HD group, a greater proportion of patients in the CAPD group received a cadaveric transplant, and many potential CAPD failures causing hospitalization and other extra costs were avoided. Also, CAPD patients with technical failure or impaired physical capability (eg, stroke, cardiac insufficiency) often had to change to HD therapy; ie, they leave CAPD when more intensive treatment is needed and cost-producing factors start accumulating. The 2 modalities are different in their cost expectations. It is unlikely that this issue of selection bias will ever be fully resolved unless patients are randomly assigned to CAPD or HD therapy. Nevertheless, the major conclusion in this study is that even without adjustments, no remarkable difference in costs between HD and CAPD could be found.

The prognosis of patients receiving a transplant was much more favorable than that of patients on dialysis therapy. During follow-up, only 3 of 55 patients died. The low death rate also affects costs: Death has an associated cost because patients with elevated risk are treated intensively. To assess lifetime costs, a much longer period of follow-up is needed, and this issue remains unanswered in our study. To our knowledge, previous studies have not evaluated lifetime costs in detail either.

Differences in the care of patients with ESRD worldwide, financing of health care systems, and dialysis modality utilization limit the generalizability of our results to other countries. Finland has a publicly funded health care system, and general health insurance is paid as income tax. Hospital costs are almost completely funded by the government and municipalities; direct payments from patients cover only an insignificant fraction of total costs. Most patient expenditures for CAPD fluids, outpatient medication, and transportation are reimbursed by health insurance. In Finland, as in other Western countries, HD is the most commonly practiced modality of RRT.³²

Home HD and self-care HD, estimated to be clearly less expensive than in-center HD,^{15,18} were not applied in the Tampere region during the study period. The number of intermittent PD and continuous cycling PD days was comparatively small in our study. The long distances between patients' homes and the dialysis center (average, 27 km) caused considerable transportation costs.

Our main motivation to undertake the study was to determine costs of various RRTs. Because total expenditures and the structure of costs are known, results also can be used to achieve savings. The most beneficial area for savings is the cost for inpatient hospitalization, and efforts should be made to reduce or shorten hospital stays. Dialysis therapy and medication are essential and not likely to be overprescribed, and the other costs are of minor significance. The matter of effectiveness is not included in the analysis, but this study emphasizes the requirement for a cost-effectiveness study evaluating RRT, and our purpose is to publish an analysis in the future by using data obtained in this study. In summary, average direct costs of CAPD patients were slightly lower than those of HD patients, but some caution has to be exercised when interpreting this result because of complexities associated with the comparison of these modalities. The lowest costs and best survival were found in the TX group, and the superiority of this modality to HD and CAPD therapy is obvious.

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Alternative strategies to evaluate the cost-effectiveness of peritoneal dialysis and hemodialysis

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Abstract

Background Dialysis treatment requires considerable resources and it is important to improve the efficiency of care.

Methods Files of all adult end-stage renal disease (ESRD) patients who entered dialysis therapy between 1991 and 1996, were studied and all use of health care resources was recorded. A total of 138 patients started with in-center hemodialysis (HD) and 76 patients with continuous ambulatory peritoneal dialysis (CAPD). Four alternative perspectives were applied to assess effectiveness. An additional analysis of 68 matched CAPD-HD pairs with similar characteristics was completed.

Results Cost-effectiveness ratios (CER; cost per life-year gained) were different in alternative observation strategies. If modality changes and cadaveric transplantations were ignored, annual first three years' CERs varied between \$41220–61465 on CAPD and \$44540–85688 on HD. If

CAPD-failure was considered as death, CERs were \$34466–81197 on CAPD. When follow-up censored at transplantation but dialysis modality changes were ignored, CERs were \$59409–95858 on CAPD and \$70042–85546 on HD. If observation censored at any change of primarily selected modality, figures were \$57731–66710 on CAPD and \$74671–91942 on HD. There was a trend of lower costs and better survival on CAPD, the only exception was the strategy in which technical failure of modality was considered as death. Figures of the matched CAPD-HD pairs were very close to the figures of the entire study population.

Conclusions Compared to HD, CERs were slightly lower on CAPD.

Keywords CAPD · Cost · Cost-effectiveness · ESRD · Hemodialysis

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Introduction

The high cost of renal replacement therapy (RRT) presents an economic and ethical dilemma for those responsible for funding treatment programs for patients with end-stage renal disease (ESRD) [1]. Sicker patients requiring more medical intervention are entering in dialysis therapy. On the other hand, scarcity of resources is a reality in present health care systems [2]. In

developed countries, it has been estimated that 1%–2% of overall health budgets are spent on ESRD care, although only 0.08% of population has ESRD [3–5].

In response to scarcity, economic evaluation has gained popularity in the field of ESRD care. There is a near unanimity of opinion that renal transplantation is far cheaper than prolonged dialysis [6]. Many studies have demonstrated its superiority when compared to dialysis therapies: It is associated with a more favorable cost-effectiveness ratio (CER) and it also results to a better quality of life [7–9]. However, consensus has not been reached on the cost-effectiveness (CE) of different dialysis modalities [10, 11]. A number of confounding factors prevent reliable comparisons between hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD): The patient selection into dialysis modalities is not randomly assigned. It is likely that patients who are sicker or healthier than average systematically select different modalities and the patients being selected to each of the therapies are different in their likely cost expectation [12] and also several non-medical factors impact on modality selection [13]. Patients also use multiple modalities over time and switching among dialysis therapies makes the modality definition complex. Many cost estimates have been derived from the imbursements by the health insurance to the dialysis centers, which do not correspond to the actual production costs but take the perspective of the payers [10, 14, 15].

We performed a CE analysis comparing in-center HD and CAPD. The cost analysis included a precise file survey containing both the direct costs for dialysis therapy and also costs for hospitalizations, medications etc. All use of health care resources and services was recorded. Valuation of cost data was based on the cost for the providers, not charges. To assess effectiveness, four different strategies were applied.

Subjects and methods

Patient's characteristics and costing procedures have been previously described in detail in our article focusing on costs and structure of costs [16].

Patients and follow-up

The study was performed at Tampere University Hospital (TaUH) in Finland. This hospital is providing care for a population of about 440,000 people. All the adult ESRD patients entering first time in RRT between January 1, 1991 and December 31, 1996 were included in the study. The follow-up started on the day dialysis therapy was first performed and continued until the end of 1996, death, loss to follow-up or renal function recovery. Altogether 214 adult patients (120 males and 94 females) entered in dialysis therapy during the study period. The diagnostic grouping and the demographic and clinical characteristics are presented in Table 1. The mean age of patients was 56.5 (± 1.0 SEM, range 15–84 years). The largest diagnostic group was diabetic nephropathy with 76 patients (33 with insulin-dependent and 43 with non-insulin-dependent, respectively). The group of chronic glomerulonephritis included 54 patients. There were 20 patients in the amyloidosis group and interstitial nephritis was found in 20 cases. In 32 cases the cause of ESRD was undefined nephropathy or secondary nephropathy other than diabetic

Table 1 Patient diagnostic grouping and demographic characteristics

Diagnostic group	Number (% of total population)	Mean age	Start on HD <i>n</i> (%)
Primary renal diseases (PRD)	86 (40)	55.3	54 (63)
Chronic glomerulonephritis (CGN)	54 (25)	52.9	29 (54)
Interstitial nephritis (INTE)	20 (9)	60.1	13 (65)
Polycystic kidney disease (POLY)	12 (5)	58.1	12 (100)
Non-primary renal disease (NON-PRD)	128 (60)	57.4	84 (66)
Diabetes (DIAB)	76 (36)	54.7	44 (58)
Amyloidosis (AMYL)	20 (9)	54.9	15 (75)
Miscellaneous nephropathies (MISC)	32 (15)	65.1	25 (78)
Total	214 (100)	56.5	138 (65)

nephropathy or amyloidosis and these patients were defined to have miscellaneous nephropathy. About 15 of them had hypertensive nephrosclerosis.

A total of 138 patients started on HD and 76 patients in CAPD. A summary of demographic data in different treatment modalities is shown in Table 2. To avoid distortion caused by different patient selection between the two modalities, we separately analyzed a sub-population with similar characteristics: For each patient on CAPD we determined a control case on HD with similar age (± 6 years) and co-morbidities. Consequently, 68 HD-CAPD-patient pairs were formed. The patient characteristics of this group are shown in Table 3. The mean age of the selected sub-population was 53.9 (both CAPD and HD) compared to 51.1 years (CAPD) and 58.6 years (HD) of the whole population.

Table 2 Summary of demographic data in different treatment modalities. Values expressed as number (%) or mean (\pm SEM)

	HD-patients (<i>n</i> = 138)	CAPD-patients (<i>n</i> = 76)	<i>P</i> (HD vs. CAPD)
Mean age (\pm SEM)	58.6 (± 1.2)	51.1 (± 1.9)	0.000
<50 years	30 (22%)	38 (50%)	0.000
Body-mass index (\pm SEM)	26.0 (± 0.42)	24.6 (± 0.46)	0.005
Male	80 (63%)	40 (53%)	0.542
Deaths	56 (41%)	16 (21%)	0.006
Transplanted	29 (21%)	26 (34%)	0.051

Table 3 Characteristics of the selected 68 matched CAPD-HD-patient pairs. Values expressed as number (%) or mean (\pm SEM)

	HD (<i>n</i> = 68)	CAPD (<i>n</i> = 68)	<i>P</i> (CAPD vs. HD)
Mean age (\pm SEM)	53.9 (± 2.0)	53.9 (± 2.0)	0.994
Deaths	26 (38%)	16 (24%)	0.095
Transplanted	20 (29%)	25 (37%)	0.466
Primary renal disease	31 (46%)	29 (43%)	0.863
Diabetics	19 (28%)	27 (40%)	0.205

Modality definition

Mode of dialysis therapy was defined on intention-to-treat basis. Patients were classified as CAPD or HD patients based on their treatment modality at the start of the study period and retained that classification even if their dialysis modality changed or if they received a cadaveric transplant over the study period. However, if CAPD was the modality planned in pre-dialysis time but a patient had to start RRT acutely with HD and switched to CAPD within 30 days, this patient was still regarded as CAPD-patient.

Costing procedures

The cost analysis was performed from the perspective of service providers and the study was designed to include the total costs of care for patients, including both dialysis related and other costs. Overhead costs due to infrastructure and administration were included. All resource use was valued at 1997 prices.

The cost for a single HD session was \$193 including solely costs for dialysis; costs of e.g., laboratory tests, intra- and interdialytic drugs and hospitalizations were excluded since they were assessed as separate categories. Normally patients received three four-hour treatments weekly. The costs of a CAPD day were \$58–\$96 depending on fluid volume and number of bag exchanges. This figure includes costs for fluids, hoses, protective caps, disinfecting, and other equipment. DianealTM and Lockolys-GlucosTM were applied as dialysis fluids and these products were utilized equally (52% and 48% of PD days, respectively). The price of most typical form (4 \times 2 l per day) was \$77 (DianealTM) and \$75 (Lockolys-GlucosTM), respectively. Continuous cycling peritoneal dialysis (CCPD) accounted for only 4.2% of total peritoneal dialysis days and therefore CCPD was analyzed under title CAPD in this study. Costs from CAPD training were included in analyses.

The daily costs of hospitalization at a general ward in TaUH, Cardiac Care Unit, and Intensive Care Unit were \$226, \$467, and \$1645, respectively. These figures contain only the “hotel” costs, thus excluding costs for medications, laboratory

tests, radiological or any other examinations. Local hospitals and health centers accounted for 20% of all hospital days and these days were valued on the basis of their total daily hospital cost. The patients' use of medication was recorded in detail. Both outpatient prescription medications and medicines during the dialysis sessions, intravenous antibiotics and liquids during hospitalizations were included. Traveling distance (on average 27 km) and frequency of traveling from and to hospital was obtained from patient files. These were valued by average taxi costs (\$0.96 for 1 km). The number of visits to different outpatient clinics and consultations during hospitalization were recorded and data on the costs were obtained from the hospital accounting system. The number of surgical operations, invasive examinations and implantations of central venous catheters were registered. Costs for arterio-venous fistula operations and peritoneal catheter implantation were included in analyses. Costs of laboratory tests were acquired from the database of the Central Laboratory of the TaUH. Costs data on diagnostic examinations (radiology, clinical physiology, nuclear medicine, pathology) which were performed during the study period, were obtained from the respective units.

Renal transplantations in Finland are centralized at Helsinki University Hospital. There, the cost for transplantation procedure was \$5150 and the daily cost of hospitalization (at aggregate level, including medications, examinations, and possible dialysis therapy) was \$756. The standard immunosuppressive therapy (combination of azathioprine, methylprednisolone, and cyclosporine) was used after transplantation. All transplants among the study population were cadaveric.

Mean costs, effectiveness, and cost-effectiveness analysis

Mean costs in different treatment modalities for a given period were obtained by dividing the observed costs in a given period by the respective number of days multiplied by the length of the period. Effectiveness was determined as probability to survive the given period. Cost-effectiveness ratios (CER; cost per life-year gained) were determined by dividing the calculated mean costs by effectiveness.

We decided to use four different strategies to determine the cut-point of follow-up: Strategy 1: Intention to treat. Patients starting either on HD or on CAPD were observed until end of follow-up time or death. Modality changes and kidney transplantation were not taken into account. Strategy 2: Death of modality: Technical failure was additionally considered as death. Follow-up continued until end of follow-up time, death, or technical failure. Strategy 3: Time on dialysis. Follow-up continued until end of follow-up time, death, and cadaveric transplantation. Strategy 4: Time on primarily selected modality: Patients were observed until modality change of any reason including cadaveric transplantation.

Statistical analysis

Patient characteristics were compared between HD and CAPD groups using Student's *t*-test for continuous variables and Spearman's chi-square test for categorical variables. Patient survival was estimated using the Kaplan–Meier method. Survival in the modalities was compared using the log-rank test.

Results

Mean follow-up time was 23 months in the HD group and 28 months in the CAPD group. Switching of modality was common: Of 76 patients on CAPD, 18 patients (24%) had to change to HD due to technical failure during the first year. There were no technical failures in the HD group, but 12 patients changed voluntarily to CAPD. 55 patients received a cadaveric transplantation, 29 of them started on HD and 26 on CAPD, respectively. Patient outcomes during consecutive yearly observations are shown in Fig. 1.

Patient survival

Altogether 72 patients (34%) died during the study period. The median time of survival for all patients was 57.7 months. Fig. 2 illustrates the survival of patients starting on HD and CAPD.

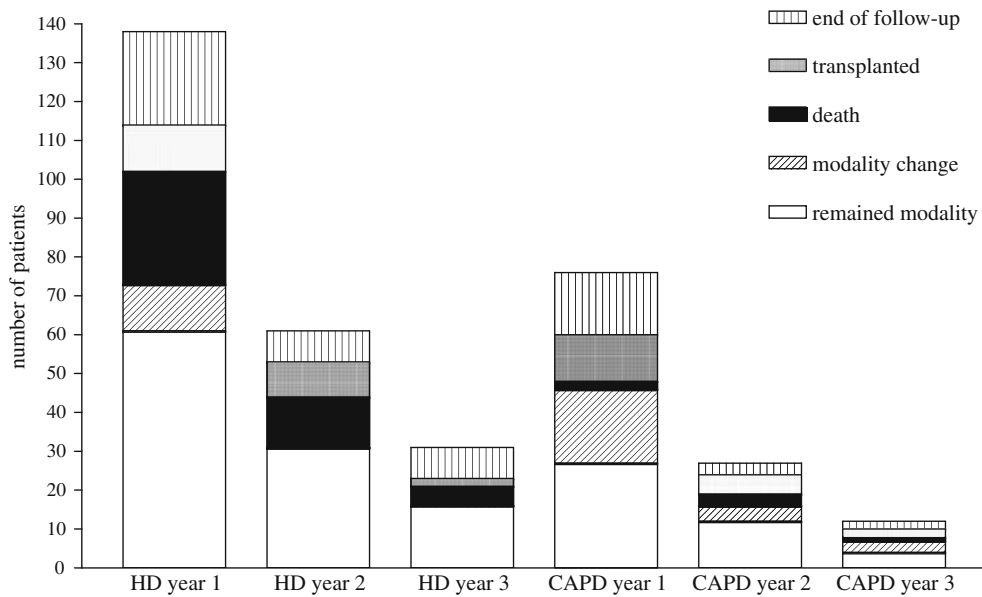


Fig. 1 Patients retention in primary treatment and modality changes between yearly observations. Situation at the end of the year

Modality changes and cadaveric transplantations were ignored. Patients on CAPD had a better survival than patients on HD ($P = 0.0025$). However, when technical failure was taken into account and considered as an end-point of follow-up, there was no difference between the modalities.

Cost-effectiveness

Cost-effectiveness ratios are shown in Table 4 and Fig. 3 for the whole population and in Table 5 and Fig. 4 for matched CAPD-HD pairs. If modality changes are not taken into account (strategy 1), costs were lower and survival was

Fig. 2 Survival on HD (solid line) and CAPD (dashed line) by Kaplan–Meier method. $P = 0.0025$ by the log-rank test

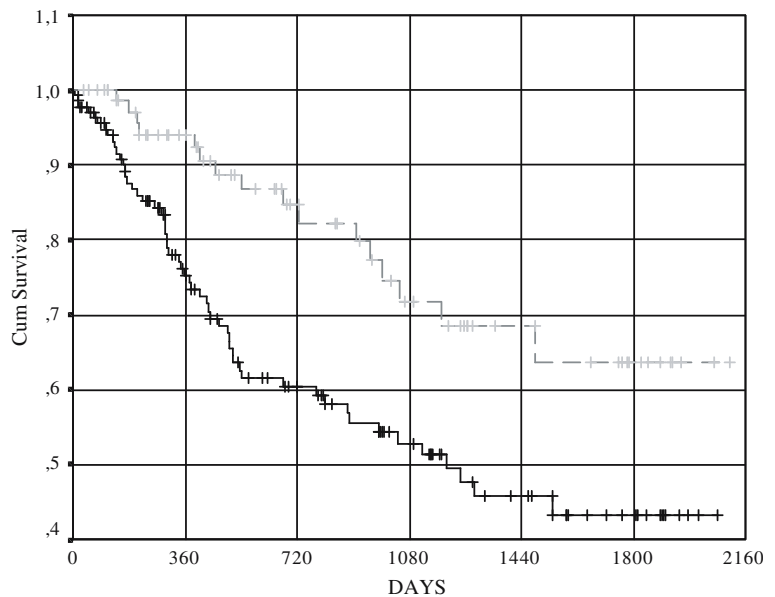


Table 4 Cost-effectiveness ratios on CAPD and HD. Costs: cumulative costs during the observation period; effectiveness: probability to survive the given period. Four different strategies were applied to determine the end-points of follow-up

		Cost CAPD	Cost HD	Eff. CAPD	Eff. HD	CER CAPD	CER HD	Incre- mental costs on HD	Incre- mental eff. on HD	Incremental CER on HD
Strategy 1	Year 1	57,845	64,463	0.94	0.75	61,465	85,688	6618	-0.19	CAPD dominates CAPD dominates 148303 CAPD dominates
	Year 2	42,288	50,868	0.90	0.80	47,023	63,300	8580	-0.10	
	Year 3	34,913	38,932	0.85	0.87	41,220	44,540	4019	0.03	
	Years 1-3	143,559	165,712	0.72	0.53	200,278	313,552	22,153	-0.19	
Strategy 2	Year 1	57,260	64,463	0.71	0.75	81,197	85,688	7203	0.05	152930 CAPD dominates 181960 444041
	Year 2	36,656	50,868	0.82	0.80	44,889	63,300	14,212	-0.01	
	Year 3	28,069	38,932	0.81	0.87	34,466	44,540	10,863	0.06	
	Years 1-3	137,249	165,712	0.46	0.53	295,540	313,552	28,463	0.06	
Strategy 3	Year 1	55,787	63,338	0.94	0.74	59,589	85,546	7551	-0.20	CAPD dominates CAPD dominates HD dominates
	Year 2	50,468	55,007	0.85	0.78	59,409	70,630	4539	-0.07	
	Year 3	62,279	55,186	0.65	0.79	95,858	70,042	-7093	0.14	
	Years 1-3	165,848	180,125	0.52	0.45	320,975	396,489	14,277	-0.06	
Strategy 4	Year 1	55,116	64,566	0.83	0.71	66,710	91,492	9450	-0.12	CAPD dominates CAPD dominates CAPD dominates CAPD dominates
	Year 2	46,491	56,689	0.81	0.73	57,731	77,486	10,198	-0.07	
	Year 3	50,519	56,705	0.80	0.76	63,149	74,671	6186	-0.04	
	Years 1-3	158,853	185,021	0.53	0.39	298,428	471,872	26,168	-0.14	

better (except year 3) on CAPD compared to HD (Table 4 and Fig. 3) and, consequently, annual and particularly cumulative first three years' CERs were more favorable on CAPD. If technical failure is considered as death (strategy 2), the average survival among CAPD-patients shortened remarkably. Cumulative first three years' CERs on CAPD and on HD were very close to each other. In strategies 1 and 2 the observation period includes time with a functioning transplant (55 patients, 26% of study population). CERs in strategy 1 were somewhat better than they were in strategies 3 and 4, in which only the time on dialysis is assessed. In strategy 3, the follow-up included only time on dialysis. Switches among HD and CAPD were ignored and there was patient flux from CAPD to HD and vice versa. Differences between costs on CAPD and on HD were not remarkable and

cumulative 3-year survival was 0.52 on CAPD and 0.45 on HD, respectively. If any change of the primary selected modality is considered as an end-point (strategy 4), costs were systematically lower and survival was better on CAPD. When assessing the selected CAPD-HD pairs (Table 5 and Fig. 4), the figures are almost identical compared to the entire population. There is a trend of lower costs and better effectiveness on CAPD. The only exception is strategy 2 with slightly lower survival on CAPD.

Data derive from 1997 and actual production costs to treat ESRD have remarkably changed since then. Between 1997 and 2004, costs for a single HD session have increased by 20%, the daily costs of hospitalization have grown by 33% and costs of visits to outpatient clinics have increased up to 50% at TaUH (data from the hospital accounting system). Costs for CAPD

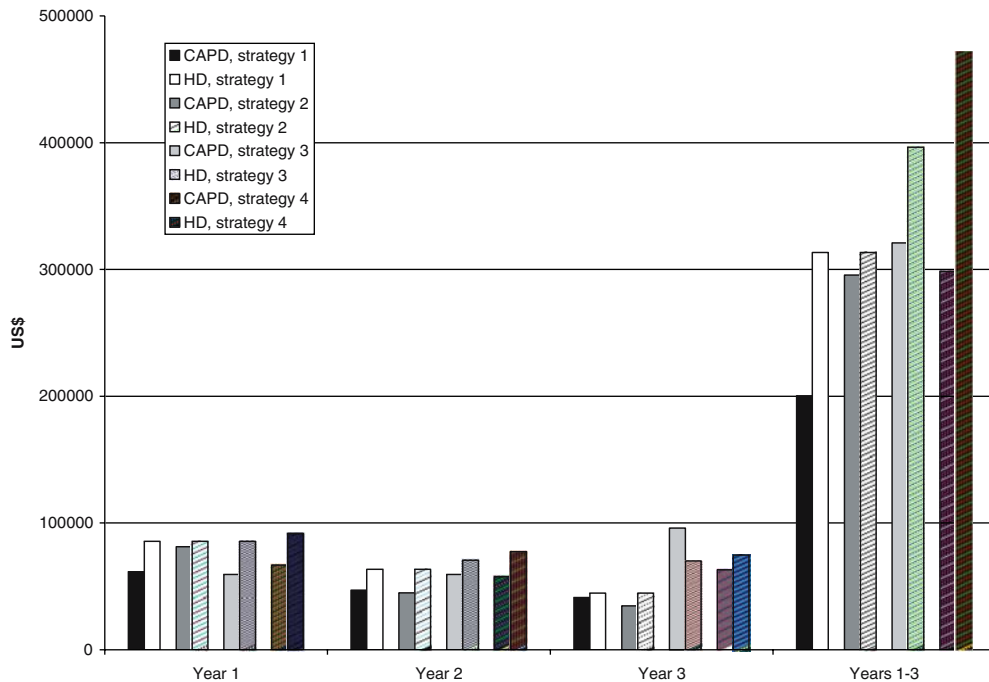


Fig. 3 Annual and first three years' cumulative cost-effectiveness ratios in different strategies

fluids and equipments were on average 15% higher in 2004 than in 1997. On the other hand, costs for prescription medications have decreased by 6% during the same time (data from the Finnish National Agency for Medicines). Expenditures for transportation were 31% higher in 2004 than in 1997. The dialysis therapy accounts for about half of total expenditures in the HD group and more than a half in the CAPD group. Costs for hospitalizations are the second largest item (14%–17% after first year on HD and 15%–18% on CAPD, respectively) and costs for medication third largest items (13%–16% on HD and 9%–14% on CAPD). [16] Based on these figures it can be estimated that the total expenditures for the given treatment have grown 22% among HD-patients and 21% among CAPD-patients.

Discussion

In our study, the average acceptance of new ESRD patients per year was 81 per million population, which is close to the rate in other developed European countries but somewhat less than for

example in Sweden [6]. Differences in financing the care of ESRD patients worldwide are remarkable. In some countries publicly funded healthcare system provides treatment, in others there are independent producers, both profit and non-profit, which are financed by supplies from health insurance institutions. Prior studies mostly have taken payers' perspective and costs have been measured by reimbursements [10, 14, 15]. The accounting methods differ between producers (for example including salaries of staff and overhead) and contracts with insurance institutions are less or more favorable, contributing to profits achieved by producers. On the other hand, serious diseases among ESRD patients result in large additional costs: hospital admission rates are high and the length of stay in hospital is prolonged, abundant medication and considerable number of surgical operations is needed compared to non-ESRD patients. In this study, we decided to take the perspective of provider because this viewpoint has rarely been reported. Cost data of all ESRD patients in a single center were obtained minutely. To our knowledge, studies with this level of accuracy in recording cost factors have not been

Table 5 Cost-effectiveness ratios on CAPD and HD. Sub-analysis of 68 matched CAPD-HD-pairs. Costs: cumulative costs during the observation period; effective-

ness: probability to survive the given period. Four different strategies were applied to determine the end-points of follow-up

		Cost CAPD	Cost HD	Eff CAPD	Eff HD	CER CAPD	CER HD	Incre- mental cost on HD	Incre- mental eff. on HD	Incremental CER on HD
Strategy 1	Year 1	58,007	65,592	0.94	0.80	61,815	81,806	7585	-0.14	CAPD dominates
	Year 2	42,876	51,822	0.90	0.78	47,789	66,464	8946	-0.12	
	Year 3	35,672	35,574	0.84	0.91	42,361	38,883	-98	0.07	
	Years 1-3	144,510	165,678	0.71	0.57	203,822	289,647	21,168	-0.14	
Strategy 2	Year 1	57,391	65,592	0.69	0.80	83,187	81,806	8201	0.11	73289 CAPD dominates
	Year 2	37,329	51,822	0.81	0.78	46,297	66,464	14,493	-0.03	
	Year 3	28,892	35,574	0.80	0.91	36,029	38,883	6682	0.11	
	Years 1-3	138,155	165,678	0.45	0.57	309,695	289,647	27,523	0.13	
Strategy 3	Year 1	55,907	634,54	0.93	0.79	59,883	80,587	7547	-0.15	CAPD dominates
	Year 2	50,467	60,755	0.85	0.73	59,408	82,897	10,288	-0.12	
	Year 3	62,279	59,650	0.65	0.81	95,873	73,843	-2629	0.16	
	Years 1-3	165,941	187,584	0.52	0.47	322,090	402,368	21,643	-0.05	
Strategy 4	Year 1	55,218	65,573	0.82	0.74	67,528	88,780	10,355	-0.08	CAPD dominates
	Year 2	46,492	64,037	0.81	0.89	57,733	71,823	17,545	0.09	
	Year 3	50,519	60,070	0.80	0.57	63,149	105,571	9551	-0.23	
	Years 1-3	158,703	194,941	0.53	0.37	301,259	520,259	36,238	-0.15	

published previously. For the first time, we determined different cut-points of follow-up to assess the effect of modality changes and cadaveric transplantation to CER.

In this study, we evaluated costs arising due to medical treatments of patients, but social sector expenditures (sickness allowances, disability pensions, home help, etc.) were excluded. Indirect costs as losses of productivity, decreased tax payments, and early retirement were also ignored, but it can be estimated, given a rather young patient population, that their impact on total expenditures is considerable.

The selection of modality is a complex decision. As the conditions of the disease, preferences of the patient technologies or physician change, the choice of modality can also change. It is unlikely that this issue of selection bias will ever be fully resolved unless patients are randomly

assigned to PD or HD. In this study, the proportion of patients starting on CAPD was 36%, whereas in the United States only 12.7% of patients are on CAPD [12]. Since the selection of a particular modality is not random, they were different in their cost expectations already at the baseline: First: Patients starting on CAPD were younger and ESRD was caused more often by chronic glomerulonephritis or type 1 diabetes. Subsequently, death rates were not equal. In this study, death rates were 41% on HD and 21% on CAPD, respectively. Death definitely has a cost associated with it: Patients with elevated risk of death are treated intensively, usually in hospital. Extra medication, operations, and invasive examinations are needed. A remarkable portion of these patients will die despite the efforts. Our finding of better survival among CAPD-patient differs from the results of a recent survey where

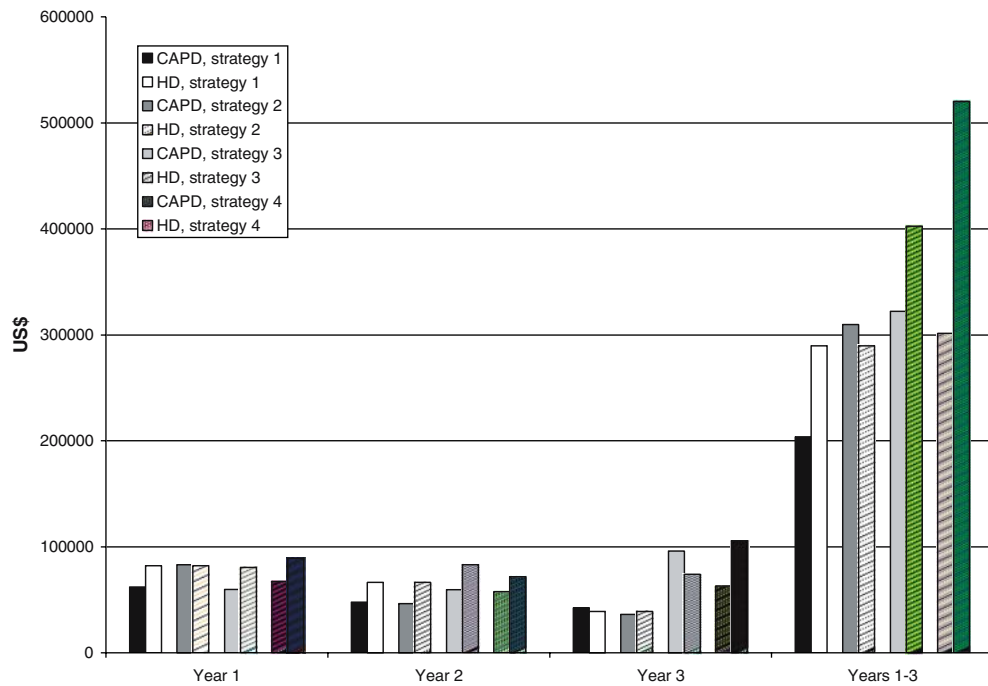


Fig. 4 Annual and first three years' cumulative cost-effectiveness ratios in different strategies. Sub-analysis of 68 matched CAPD–HD pairs

the risk for death of patients treated with peritoneal dialysis after 2 years of dialysis was twice that of patients treated with HD [17]. Contrary to our study, follow-up censored at transplantation. Second: A greater proportion of patients in the PD group were transplanted and many potential PD-failures causing extra costs were thus avoided. Third: PD-patients with technical failure or with impaired physical capability had often to change to HD; they left PD when more intensive treatment was needed. Of 76 patients on PD, 18 were forced to switch to HD due to technical failure and another 12 patients were transplanted during the first year of follow-up. On the other hand, 12 HD patients voluntarily changed to CAPD.

By determining the alternative end-points of observation, different aspects are offered to economically evaluate ESRD. If modality changes are not taken into account and the observation period includes time with a functioning transplant, second and third year's CERs were somewhat better compared to strategies in which only time on dialysis is assessed. The fact that renal transplantation yields more favorable CE than dialysis therapy has been previously demon-

strated in several studies [7–9]. Interestingly, annual costs between strategies 3 and 4 were very close to each other. Consequently, changing the modality does not have any major effect on treatment costs; they seem to be about the same level before and after modality switch.

Due to patient selection, a comparison between CAPD and HD is difficult. Instead of extended statistical processing of data and adjusting for co-morbidities, age and other covariates, we decided to select a sub-population of patients with similar characteristics: costs and life-years gained among 68 matched HD-CAPD pairs were assessed. Interestingly, despite excluding the group of HD patients (70 patients) with higher mean age, the CER of the selected HD patients did not significantly differ from CER among the whole HD population. Since the sub-analysis included almost all (68 out of 76) CAPD-patients, CERs were almost identical compared to the whole CAPD population. Likewise among the whole study population, CERs were systematically but slightly lower on CAPD than on HD. For selected patients, CAPD seems to be a more cost-effective dialysis modality than HD.

Several factors limit interpreting the results of this study. Differences in funding of healthcare systems and in dialysis modality utilization restrict the exploitability of our results to other countries. Also, costs to treat ESRD have changed remarkably since 1997. However, as the treatment costs have increased similarly in the both modalities, we can presume that slightly better CER on CAPD compared to HD still exists. ESRD patients' treatment has continuously developed, but we believe that the structure of the costs nowadays does not distinctly differ from 1997. Frequency of HD sessions or fluid volumes on CAPD have not changed since 1990s, and problems which caused hospital stays then would presumably lead to hospitalization today as well. Due to application of new and expensive medications and the routine use of erythropoietin therapy there probably have occurred an increase in the medication costs, but it affects equally both modalities. All the HD patients in this study were treated solely with in-center HD which has been reported to be more costly than home HD and self-care HD [10]. Also continuous cycling peritoneal dialysis (CCPD) has gained popularity in the last few years while the proportion of CCPD days was relatively small (4.2% of total peritoneal dialysis) in our study. A greater amount of dialysis fluids and a considerable number of other equipments are needed in CCPD compared to CAPD and it can be estimated that dialysis costs are on average about 40% higher on CCPD than on CAPD.

Treating ESRD is expensive and the number of patients is increasing rapidly. Older and sicker patients enter dialysis therapy. It is important to develop strategies for more efficient care [10]. In summary, in our single-center study, we found that CAPD was somewhat more cost-effective than HD but caution has to be exercised when the results are interpreted. Choosing between the modalities is a complex decision, where both medical and non-medical factors attribute selection.

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Implications of Levels of Serum Mineral Metabolism Markers, Albumin and C-Reactive Protein for Treatment Costs of Patients on Maintenance Dialysis

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Key Words

Albumin · C-reactive protein · Maintenance dialysis costs · Mineral metabolism

Abstract

Background: Secondary hyperparathyroidism, malnutrition and inflammation have been reported to associate with adverse outcomes in dialysis patients. However, little is known about the implications of these conditions for treatment costs. **Methods:** The cost data of all adult patients who had entered dialysis therapy at Tampere University Hospital between 1991 and 1996 and had remained on dialysis for at least 1 year were collected. Results of measurements of parathyroid hormone (PTH), calcium, phosphorus, albumin and C-reactive protein (CRP) were obtained from the database of the hospital. **Results:** Patients (n = 109), aged 57.0 ± 14.9 years, included 57% men and 37% diabetics; 62% started on hemodialysis and 38% on peritoneal dialysis. Average daily costs were USD 161 (range 95–360). After controlling for patients' age, body mass index, gender, dialysis modality and primary renal disease, there was a positive correlation between average CRP and average costs and a negative correlation between albumin and costs. Correlations between mineral metabolism markers and costs were not found, but there was a trend towards lower cost among patients who achieved the Kidney Disease Outcomes Quality Initiative tar-

gets of calcium, phosphorus and PTH (USD 145 ± 31) compared with those with nonoptimal levels (USD 165 ± 48 ; $p = 0.095$). Costs of patients with at least one in-target PTH measurement were lower than costs of patients with constantly low PTH (USD 148 ± 31 vs. 170 ± 48 ; $p = 0.01$). **Conclusion:** Serum levels of albumin and CRP correlated with dialysis patients' treatment costs. Achieving the Kidney Disease Outcomes Quality Initiative targets may be associated with lower costs.

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Introduction

Patients undergoing maintenance dialysis therapy have a high prevalence of secondary hyperparathyroidism (SHPT) [1], and a significant proportion also experience protein energy malnutrition and inflammation [2]. SHPT is characterized by increased serum levels of parathyroid hormone (PTH) and develops in response to an imbalance in serum levels of calcium (Ca), phosphorus (P) and vitamin D, as a result of altered metabolism in chronic kidney disease [3]. Disordered Ca, P and PTH concentrations are associated with increased risks of soft tissue and cardiovascular calcifications and mortality and hospitalization caused by cardiovascular disease [4–7]. Uremic bone disease (renal osteodystrophy) is another

Table 1. Demographic characteristics and average costs of 109 dialysis patients

Mean age \pm SD, years	57.0 \pm 14.9
Males	62 (57)
Diabetics	40 (37)
Primary renal disease as a cause of ESRD	45 (41)
Start on hemodialysis	68 (62)
Dead	35 (32)
Mean body mass index \pm SD	25.8 \pm 4.7
Mean daily costs \pm SD, USD	161 \pm 46

Figures in parentheses are percentages. ESRD = End-stage renal disease.

er important consequence of SHPT [8], and there is an association between risks of hip and vertebral fractures and PTH concentration [9]. Over recent years, there has been an increasing realization that the regulation of PTH secretion together with the maintenance of Ca, P and Ca \times P product within target levels [3, 10] may reduce morbidity and mortality in patients with SHPT.

The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend strict targets for the control of serum levels of PTH, Ca, P and the Ca \times P product: PTH 16.5–33.0 pmol/l (150–300 pg/ml), Ca 2.10–2.37 mmol/l (8.4–9.5 mg/dl), P 1.13–1.78 mmol/l (3.5–5.5 mg/dl) and Ca \times P product <4.4 mmol²/l² (<55 mg²/dl²) [11]. Many patients have suboptimal control of PTH and minerals. In the Dialysis Outcomes and Practice Patterns Study, about 50% of dialysis patients were below the low target for PTH, whereas the upper level was exceeded in 19–31% of patients within each country [12].

Protein energy malnutrition and inflammation are other common disturbances among hemodialysis patients. They often occur concomitantly, and due to the association with atherosclerotic cardiovascular disease, they have been referred to as ‘malnutrition inflammation atherosclerosis’ [13] or ‘malnutrition inflammation complex syndrome’ [14]. Malnutrition inflammation complex syndrome is reported to correlate with a poor outcome, including significantly greater rates of hospitalization and mortality in hemodialysis patients [2, 13, 14]. A low serum albumin level is associated with malnutrition and is a well-established predictor of mortality [4, 15] and inflammation and can be assessed by means of inflammatory biomarkers, of which CRP is the single most used.

Despite accumulating evidence that imbalance in mineral metabolism, malnutrition and inflammation

have a major effect on mortality and morbidity in dialysis patients, little is known about the effect on treatment costs. We have performed an analysis evaluating the association between costs and the commonly measured variables Ca, P, PTH, albumin and CRP in dialysis patients.

Subjects and Methods

Patients and Follow-Up

The study was performed at Tampere University Hospital, which provides care for a population of about 440,000 people. Altogether 214 adult patients entered dialysis therapy between 1 January 1991 and 31 December 1996. Of these, 111 patients remained on dialysis for at least 1 year. There were 2 patients with no available laboratory results and they were excluded from the analysis. The follow-up started on the day the dialysis therapy was first performed and continued until the end of 1996, death or kidney transplantation. Patients were classified as hemodialysis and continuous ambulatory peritoneal dialysis on an intention-to-treat basis. Their files were studied retrospectively, and the use of health care resources and services was recorded.

Costing Procedures and Laboratory Evaluation

The study was designed to include the total costs for treating dialysis patients. Both dialysis-related and other costs (medication, hospitalization, transportation, operations and invasive examinations, laboratory tests and radiological examinations) were included. All resources used were valued at the prices common in 1997. Patients’ characteristics and costing procedures have been described in detail in our article focusing on costs and the structure of costs [16]. A single patient’s average daily costs were calculated by dividing the patient’s observed total costs by the respective number of days. The results of laboratory tests performed during the study period were obtained from the database of the Tampere University Hospital. Blood tests had been taken by the decision of clinicians as a part of normal treatment and follow-up. Ca, P, PTH, CRP and albumin were routinely measured once in 3 months, and additional tests were taken when needed.

Statistical Analysis

Comparisons between groups were made by Levene’s test for equality of variances. Categorical variables were compared using the χ^2 test. Data are expressed as means \pm SD or medians. Correlations between continuous values were assessed using Spearman’s and Pearson’s correlation coefficient for nonparametric and parametric data, respectively. Partial correlation coefficients after controlling for clinical characteristics were performed using SPSS (SPSS Inc., Chicago, Ill., USA).

Results

Patients’ demographic characteristics are shown in table 1. There were 62 men and 47 women in the study, and the mean age of the 109 patients was 57.0 years (range

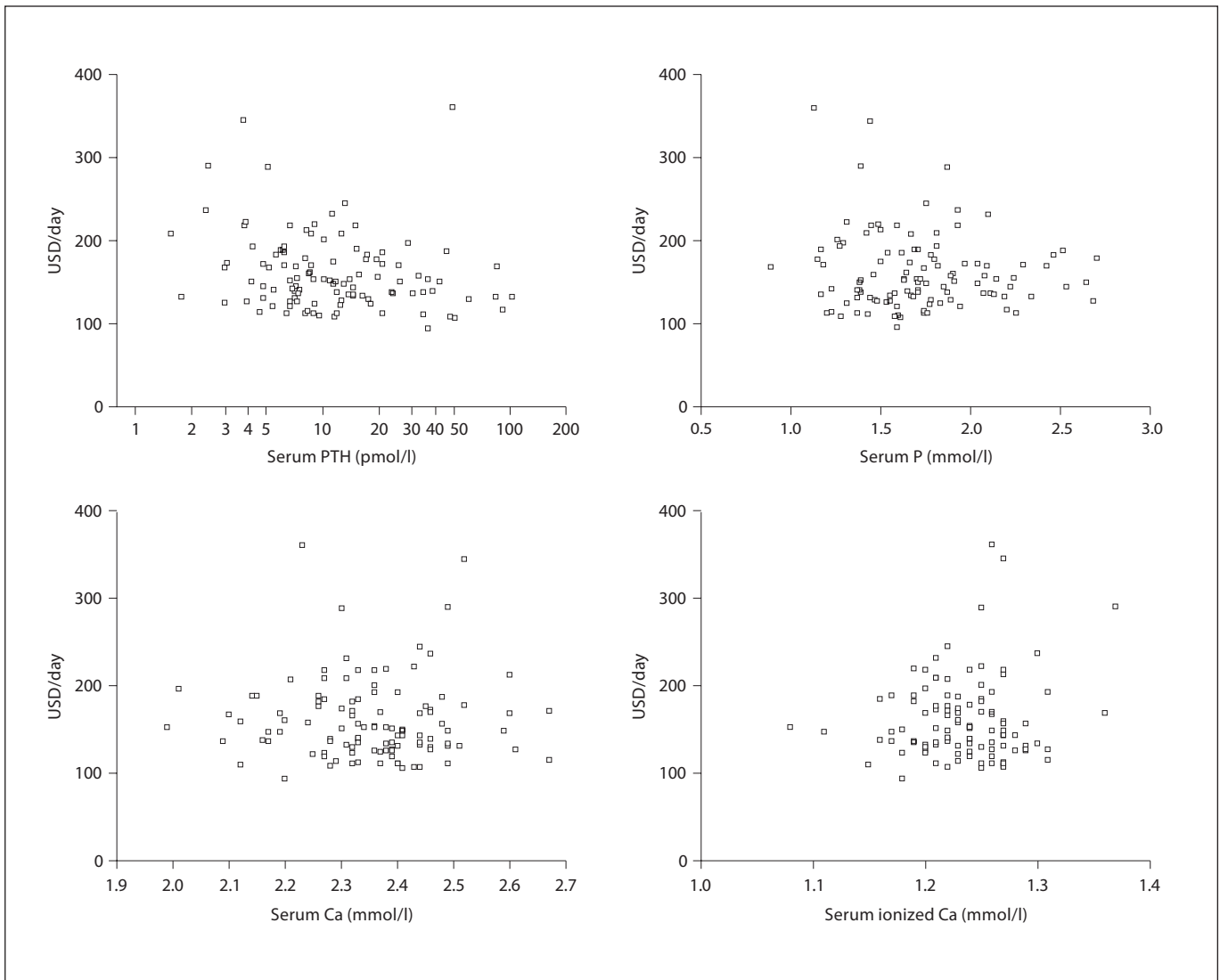
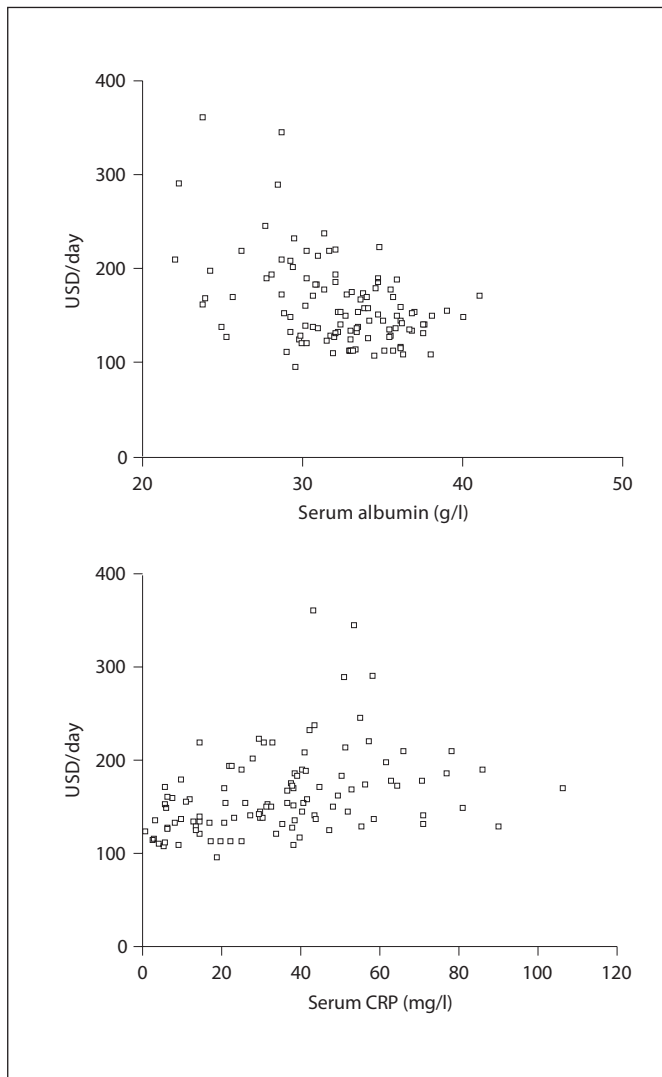


Fig. 1. Scatterplots of patients' average PTH, P and Ca levels versus average daily costs. Please note the logarithmic axis representing PTH values.

Table 2. Number and average results of laboratory tests taken during the follow-up

	Measurements	Average number of measurements/patient/year	Mean \pm SD
Serum total Ca	1,161	4.7	2.4 \pm 0.13 mmol/l
Serum PTH	1,193	4.8	16.8 \pm 18.7 pmol/l
Serum P	6,096	24.5	1.7 \pm 0.37 mmol/l
Serum ionized Ca	6,408	25.8	1.3 \pm 0.05 mmol/l
Serum albumin	2,173	8.7	32.3 \pm 3.8 g/l
Serum CRP	5,098	20.5	34.8 \pm 22.1 mg/l



16–80). Diabetics comprised 37% of the study population, and in 41% of patients, end-stage renal disease was caused by primary renal disease (chronic glomerulonephritis, interstitial nephritis or polycystic kidney disease). Sixty-two percent of patients started on hemodialysis and 38% on continuous ambulatory peritoneal dialysis. Thirty-five patients (32%) died during the follow-up. The mean follow-up time on dialysis was 832 days, and the total follow-up period includes 248 patient-years. Patients' average daily costs were USD 161 (median 151, range 95–360).

The total number of laboratory tests and results (mean \pm SD) of laboratory tests are shown in table 2. Figure 1 shows the association between patients' costs and mineral metabolism parameters. Each plot represents an individual patient's average laboratory result versus average daily costs. In 77 patients (71%), the average PTH was below target level (16.5 pmol/l) and exceeded the target level (33.0 pmol/l) in only 16 patients. Due to the domination of low PTH values, the logarithmic axis representing PTH levels is used.

Table 3 shows the relationships between costs, given laboratory parameters, age and body mass index. There was a weak negative correlation ($r = -0.221$, $p < 0.05$) between costs and PTH. Serum albumin levels and costs were inversely correlated ($r = -0.338$, $p < 0.01$), and a positive correlation was found between average CRP and costs ($r = 0.464$, $p < 0.01$) (fig. 2).

Fig. 2. Scatterplots of patients' average albumin and CRP versus average daily costs.

Table 3. Correlation coefficients between costs, laboratory parameters, age and body mass index

	Costs	PTH	CRP	Albumin	P	Ca	Ionized Ca	Age	BMI
Costs	1.000								
PTH	-0.221*	1.000							
CRP	0.464**	-0.024	1.000						
Albumin	-0.338**	0.164	-0.360**	1.000					
P	-0.002	0.110	-0.112	0.172	1.000				
Ca	-0.077	0.001	0.071	0.396**	0.269**	1.000			
Ionized Ca	-0.048	-0.086	-0.044	0.099	0.142	0.563**	1.000		
Age	0.005	-0.059	0.201*	0.003	-0.322**	0.075	-0.001	1.000	
BMI	0.152	-0.090	0.168	0.149	0.055	0.262**	0.151	0.215*	1.000

BMI = Body mass index.

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

Table 4. Subgroups of patients according to PTH level

Group	Patients	Mean average PTH ± SD pmol/l	Mean average costs ± SD USD
PTH constantly <16.5 pmol/l	59 (54.1)	8.4 ± 5.6	170 ± 48
PTH 16.5–33.0 pmol/l	43 (39.4)	22.3 ± 16.0	148 ± 31*
PTH constantly >33.0 pmol/l	7 (6.4)	64.5 ± 34.8	172 ± 85

Figures in parentheses are percentages.

* p = 0.01 compared with PTH constantly <16.5 pmol/l.

Table 5. Correlation coefficients after controlling for age, body mass index, gender, dialysis modality and primary renal disease

	Costs	PTH	CRP	Albumin	P	Ca	Ionized Ca
Costs	1.000						
PTH	-0.1369	1.000					
CRP	0.3251**	0.0602	1.000				
Albumin	-0.4680**	0.1118	-0.3785**	1.000			
P	-0.0230	0.1575	0.0054	0.1903	1.000		
Ca	0.0274	0.2004*	0.0689	0.3287**	0.2654**	1.000	
Ionized Ca	0.1379	0.0841	-0.0087	0.0361	0.0574	0.6226**	1.000

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

We divided patients into 3 subgroups according to their PTH status: (1) PTH constantly below target (<16.5 pmol/l), (2) at least one in-target result (16.5–33.0 pmol/l) during the follow-up, and (3) constantly elevated (>33.0 pmol/l) PTH. Number of patients and average costs in different subgroups are shown in table 4. There were no patients with persistently optimal PTH measurements. Average costs were significantly higher when PTH was continuously suppressed (USD 170 ± 48) compared with the group with at least one in-target PTH (USD 148 ± 31; p = 0.01). Costs in the high-PTH group were at the same level (USD 172 ± 85) as those in the low-PTH group, but there were only 7 patients with continuously elevated PTH levels, and the difference did not reach statistical significance (p = 0.18).

There were 19 patients with near-optimal (K/DOQI recommendations) mineral metabolism levels: both average Ca between 2.1 and 2.4 mmol/l and average P between 1.1 and 1.8 mmol/l and, furthermore, at least one PTH measurement between 16.5 and 33.0 pmol/l. Com-

pared with 90 patients with nonoptimal levels, albumin and CRP levels of these 19 patients were equal, and no significant differences in patient characteristics (age, gender, diabetes, primary renal disease, body mass index) or mortality were found. Costs of patients with near-optimal levels of mineral metabolism markers were on average USD 145 ± 31 compared with USD 165 ± 48 with nonoptimal measurements (p = 0.095). An additional analysis comparing patients with in-target Ca with non-optimal Ca and in-target P with nonoptimal P was done, and there were no statistically significant differences in costs.

After controlling for age, body mass index, gender, dialysis modality and primary renal disease, there still remained a significant correlation between costs and albumin and between costs and CRP, but PTH turned out to be statistically insignificant (table 5).

Discussion

In this study, we evaluated costs arising in medical treatment of patients. Cost data of patients were collected minutely. Social sector expenditures and indirect costs (loss of productivity, early retirement) were out of scope of this study and thus ignored. The dialysis therapy accounted for about half of total costs. Costs for hospitalizations were the second largest (on average 14–18%) and costs for medication the third largest (9–16%) items. Despite the considerable number of laboratory tests, surgical operations, radiological and other examinations, their impact on total costs was only marginal.

We found no significant correlation among mineral metabolism markers and costs, contrary to our stated hypothesis. Abnormalities in these biochemical markers have been associated with increased mortality [5, 7], and a significant association between higher serum phosphate concentration and risk of hospitalization for hip and femur fractures was also found in a large US study [17]. Supersaturation of extracellular Ca and P may accelerate the development of medial wall vascular calcification, known to be associated with increases in arterial stiffness, aortic pulse wave velocity and left-ventricular size [18]. Logically, disturbances in mineral metabolism markers could be expected to associate with higher costs as well.

There are several possible explanations for these results. First, the distribution of PTH values was dominated by values below the target, and the amount of patients with constantly elevated PTH was low. Possibly, the uneven distribution biases results. Second, data were derived from the 1990s, and the patients' SHPTs were managed by large doses of Ca-containing phosphate binders, which in turn may lead to Ca loading and soft-tissue and cardiovascular calcification. At the time of the study, the target of serum Ca concentration was the upper normal margin. Currently, newer phosphate binders have been introduced. Third, parameters vary over time, and the reported average value may be subject to misclassification bias. We cannot claim that average values or costs remain the same throughout the study period. Fourth, only 109 patients were included in this study, and due to comorbidities, the average daily costs between patients varied significantly. Theoretically, few outliers could affect results and give misleading information. However, in 90% of patients, the average daily costs were between USD 95 and 213, and after excluding the decile of patients with the highest costs from the analysis, the results did not change.

Even though there was no direct correlation between Ca, P or PTH and costs, there was a trend towards lower

costs among patients with in-target results of all three mineral metabolism markers (Ca, P and PTH), compared with patients with off-target results. Recommended Ca or P levels alone were not linked with costs, whereas on the contrary, the PTH level was. Continuously low PTH was associated with higher costs compared with patients with at least occasionally in-target PTH. Average costs in patients with continuously high PTH were at the same level as costs in the high-PTH group, but the number of patients with constant SHPT was small. Thus, a significant difference compared with patients with in-target PTH could not be found.

Retrospective analysis can be criticized as an inappropriate method to assess correlations between laboratory values and costs. However, our approach is supported by the finding that both CRP and albumin were statistically significantly correlated with costs. Serum CRP, as an acute-phase protein, strongly correlated with costs. In this study, CRP may be rather considered as a marker of infection than a marker of inflammation. In a retrospective setting, CRP was frequently measured when the patient was treated due to infections, and elevated CRP values were obtained in patients with poor general condition, high hospitalization rates, use of intravenous antibiotics and, consequently, high costs. The correlation with costs and CRP was strong, even when median CRP was used instead of average CRP.

Hypoalbuminemia results from the combined effects of inflammation and inadequate protein and caloric intake in dialysis patients, and serum albumin is a known predictor of mortality in dialysis patients [4]. A significant inverse correlation between costs and albumin was found in this study. Undoubtedly, albumin is an important factor for poor clinical outcome of dialysis patients.

To our knowledge, our study is the first one to evaluate the association between costs and mineral metabolism markers, CRP and albumin. SHPT, hypoalbuminemia and elevated CRP are all associated with adverse outcomes. Traditional therapies for SHPT are limited by side effects that may place patients at higher risk of vascular calcification. The calcimimetic cinacalcet has been effective and well tolerated in the management of SHPT, and it has been shown to have favorable effects on clinical outcomes in patients with chronic kidney disease [19]. Preliminary results of the Dialysis Clinical Outcomes Revisited Study have shown a significant decrease in mortality and hospitalization in patients receiving sevelamer hydrochloride compared with Ca-based phosphate binders. However, so far, no studies have evaluated the effect of treating SHPT on costs. In this study, we assessed the im-

pact of commonly measured laboratory markers on the costs of dialysis patients. In conclusion, serum levels of albumin and CRP were associated with the treatment costs of dialysis patients. There was no direct correlation between costs and mineral metabolism markers, but a trend towards lower costs in patients who achieved the K/DOQI targets was found.

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STRUCTURED OUTPATIENT PERITONEAL DIALYSIS CATHETER INSERTION IS SAFE AND COST-SAVING

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◆ **Background:** Data about outcomes and costs for peritoneal catheter insertion on an outpatient basis are scarce.

◆ **Methods:** Using patient files, all peritoneal dialysis (PD) catheter insertions performed between 2004 and 2009 in a single-center tertiary care institution for adult patients were located. Patient demographics, complications, hospitalizations, survival, and treatment modality changes were recorded. Procedure-related expenses were valued as actual production costs.

◆ **Results:** During the study period, 106 PD catheters were inserted. In 46 cases, the patients were admitted electively for catheter insertion; 19 catheters were placed during admission for other medical reasons; and 41 catheters were placed on an outpatient basis. Among the study patients (54.7 ± 16.0 years of age), 45% were diabetic. Early (<30 days) catheter-related complications occurred in 22% of patients. The incidences of technique failure and any complication within 90 days were 10% and 38% respectively. The occurrence of complications was not statistically significantly different for outpatients and electively admitted patients. Average costs for catheter insertion were higher in electively hospitalized patients than in outpatients (€2320 ± €960 vs €1346 ± €208, $p < 0.000$).

◆ **Conclusions:** Compared with an inpatient procedure, outpatient insertion of a PD catheter results in similar outcomes at a lower cost.

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KEY WORDS: Peritoneal dialysis catheter; insertion; outpatients; peritonitis; technique failure; costs.

Protocols for peritoneal dialysis catheter insertion (PDCI) vary. Traditionally, many units admit patients for catheter placement. However, insufficiency of resources

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has led to an increased need to alleviate the high demand for hospital beds (1), and implementing same-day surgery for various procedures has gained popularity.

So far, data to support PDCI on an outpatient basis are scarce. In a short report in 2002, Verrelli *et al.* (1) described the 3-month follow-up of 196 PDCIs in a single Canadian center. Of the PDCIs, 90 were performed on an outpatient basis, and compared with inpatient insertions, the outpatient insertions showed no differences in complication rates. In another short report in 2002, Chang *et al.* (2) reported a 10-year experience of outpatient catheter placement at a single institution. Among 251 catheters placed in 225 patients, same-day surgery was used in 165 cases. Catheter survival with same-day surgery was 84% at 1 year, and 18 catheter-related complications occurred within the first week. The authors of those two reports concluded that PDCI can safely be performed on an outpatient basis.

Hospitalization demands resources, and it also contributes substantially to the costs of treating dialysis patients (3). Considerable savings could be achieved by reducing unnecessary admissions. However, no available publications have compared costs for inpatient and outpatient PDCI. The present study analyzed PDCIs performed in a single tertiary care center with the aim of describing the outpatient PDCI protocol and comparing the short-term outcomes and costs of inpatient and outpatient PDCI.

METHODS

The patients were recruited from the Department of Medicine at Tampere University Hospital, which is a tertiary-care teaching hospital hosting the only PD program in the region, which has 450 000 inhabitants. All PDCIs for adult patients between 1 January 2004 and 31 December 2009 were included in the study. Follow-up started the day the PDCI was performed.

Data were collected from patient files held in an electronic database. The diagnostic classification used was based on the cause of end-stage renal disease obtained from the files. Patient demographics, incidence of infectious complications (peritonitis and catheter-related infections), noninfectious complications (catheter-related mechanical complications, leaks, and other problems), hospitalizations, and survival and treatment modality changes were recorded. Complications were divided into those occurring early (≤ 30 days) and late (> 30 days) after the PDCI procedure. Technique failure was defined as transfer to hemodialysis therapy because of peritonitis, ultrafiltration failure, inadequate dialysis, exit-site or tunnel infection (or both), or mechanical problems.

A single-cuffed catheter was used for all patients. Procedures were performed by surgeons, usually with the patient under spinal anesthetic in the operating room. Vital signs, electrocardiogram, and pulse oximetry were monitored throughout the operation. The conventional open minilaparotomy technique was used in all cases, with a single midline infraumbilical incision 4 – 6 cm in length. The catheter was passed through this incision on a straight introducer into the well of the pelvis and was secured with a purse-string suture in the parietal peritoneum. The linea alba was closed with a suture and the catheter was tunneled to an exit site in the iliac fossa. After demonstration of good inflow and outflow and an absence of fluid leaks, the wound was closed.

Patients scheduled for inpatient PDCI were admitted directly to the nephrology ward 1 day before the procedure. They were discharged on the first postoperative day unless there was a need for further hospitalization. After discharge, patients visited weekly with the PD nurse, and PD training was started within 4 weeks of catheter insertion.

Outpatient PDCIs were initiated in September 2006. Table 1 shows the critical pathway for outpatient PDCI in detail. Eligible patients were selected and referred by nephrologists at Tampere University Hospital. Before the procedure, patients visit the nephrology outpatient clinic, where a history and physical examination are performed, and the risks and benefits are discussed. Blood samples are taken to determine cell count and chemistry. Patients are scheduled for catheter insertion within 1 week of their visit. They are advised not to eat after midnight on the day of the procedure. Bowel preparation is not needed. The procedure is started in the morning, and once it is finished, patients are taken to the recovery room. Based on the nephrologist's decision, patients are discharged once they have had lunch, have been able to ambulate, and have voided urine. The usual time of discharge is about 15:00 h.

Our economic analysis took the perspective of a service provider. The resources and services were valued as actual production costs. Costs of PDCI, outpatient visits, and 1 day's hospitalization at the nephrology department were obtained from the administrative department of Tampere University Hospital. All resource use was valued at 2010 prices.

Data are expressed as mean \pm standard deviation unless otherwise stated. Patient characteristics were compared using the t-test for continuous variables and the chi-square test for categorical variables. Survival was estimated using the Kaplan–Meier method. Patient survival was defined using the endpoints of death, censoring at study end, or withdrawal from peritoneal dialysis by a living patient because of a change to hemodialysis or because of kidney transplantation. When considering the survival of catheters, survival was defined as technique failure, censoring at the end of the study period, death, or kidney transplantation. Survival between groups was compared using the log-rank test.

RESULTS

Between 1 January 2004 and 31 December 2009, 106 PDCIs (65 in men, 41 in women) were performed at our institution. Of those 106 PDCIs, 6 represented a second procedure in a patient who had already undergone PDCI. Of all the PDCIs, 65 were performed on hospitalized patients. Of those 65 patients, 46 had been admitted electively for PDCI (group A: elective hospitalization), and 19 patients had received their catheter during an admission because of late referral and a need to start renal replacement therapy immediately, or during an admission for other medical reasons (group B: other hospitalization). The remaining 41 patients received their catheters on an outpatient basis (group C: outpatients).

Mean age of the patients was 54.7 ± 16.0 years (range: 20 – 91 years). Diabetic nephropathy was the cause of end-stage renal disease in 45% of patients, and chronic glomerulonephritis, in 25%. Table 2 summarizes demographic data for the patients.

Patients who underwent PDCI during hospitalization for other medical reasons (group B) were older ($p = 0.032$) than patients hospitalized electively for PDCI (group A). We observed no statistically significant differences in male-to-female ratio, body mass index, or presence of diabetes between the groups.

Early complications (at ≤ 30 days) occurred in 23 patients (22%) overall, with an equal incidence in the outpatient and electively hospitalized groups (22% and 22% respectively, Table 3). Of all early complications, 13 were infectious in nature (5 peritonitis

TABLE 1
Critical Pathway for Outpatient Peritoneal Dialysis (PD) Catheter Insertion

Preoperative office visit

- Patient history and physical examination
- Education of patient about general goals and expectations, discussion of risks and benefits
- Instructions for meals and medication: No meals after midnight before the operation, medication should be taken in the morning
- Blood sample: cell count, electrolytes, creatinine, C-reactive protein, international normalized ratio, activated partial thromboplastin time
- Nasal mupirocin ointment for 5 days preoperatively

Day of operation (within 1 week of preoperative office visit)

- Before the operation (07:45 h)
 - Patient history: meals, medications, general condition
 - Blood pressure and blood sugar (diabetic patients)
 - Intravenous line inserted, prophylactic antibiotic (cefuroxime 1.5 g) started
 - Patient transferred to operating room with PD catheter set and supplies and 2000 mL 1.36% dextrose dialysate
- PD catheter insertion procedure (operating room, 08:30 h)
- After the operation (recovery room, 10:00 h)
 - Blood pressure monitoring, blood sugar measurements (diabetic patients)
 - Catheter flushed 1–2 times with 1000 mL 1.36% dextrose dialysate
 - Exit site and incision are checked to detect leaks or bleeding
 - Instructions for post-implantation care: The dressing applied should be kept dry and should not be changed (except in the presence of bleeding or infection) before the postoperative visit at 1 week

Lunch (noon)

- Patient is encouraged to ambulate and void urine after having recovered from anesthesia
- Treatment of postoperative pain
- Discharge (upon nephrologist's decision after clinical examination, 15:00 h)

Postoperative visits

- Weekly controls by PD nurse: Aseptic management of the exit site and incision; sutures removed after 7–10 days
- Mupirocin cream at exit site
- Patient education: Catheter and exit site management
- Dressing changes once weekly during the first week, and every 2 to 3 days thereafter
- PD is usually started 2–4 weeks after catheter insertion
- Permission to shower after 1 week

episodes, 8 exit-site infections). An early pericatheter leak occurred in 1 patient, and 9 patients experienced mechanical or bleeding complications. Immediate postoperative complications occurred in 4 patients, 3 of them being in the outpatient group (7%). These patients needed short-term hospitalization. None of the complications was life-threatening; all patients were discharged within 48 hours, no procedure-related deaths occurred.

Technique failure within 90 days occurred in 11 patients (10%), and some form of complication within 90 days occurred in 40 (38%). Infectious complications occurred in 26 patients (25%). Differences in complication rates were statistically insignificant between outpatient and electively admitted patients, but we

observed a trend toward a lower number of infectious complications in the outpatient group ($p = 0.080$).

The overall incidence of technique failure during the entire follow-up period was 0.29 per patient-year, and the rates of peritonitis and of peritonitis and catheter-related infections combined were 0.68 and 0.88 per patient-year respectively. Cadaveric kidney transplantation was performed in 36 patients, and 18 patients died during the study period. Compared with the electively hospitalized patients, patients hospitalized for other medical reasons experienced higher mortality ($p = 0.029$).

Figure 1 shows catheter survival for the first year in the various groups. Differences between the groups were not statistically significant ($p = 0.794$, group A vs group C).

TABLE 2
Baseline Patient Characteristics

Variable	Overall (n=106)	Patient group			p Value (A vs C)
		A: Elective hospitalization (n=46)	B: Other hospitalization (n=19)	C: Outpatient (n=41)	
Mean age (years)	54.7±16.0	52.3±16.5	63.3±14.9 ^a	53.4±14.9	0.752
Sex [n (% men)]	65 (61)	31 (67)	11 (58)	23 (56)	0.278
Mean body mass-index (kg/m ²)	24.8±4.1	25.0±4.1	25.0±5.2	24.4±3.5	0.461
Mean follow-up (days)	454±342	504±358	297±298	470±330	0.655
Diabetic nephropathy [n (%)]	48 (45)	20 (43)	6 (32)	22 (54)	0.343

^a $p = 0.039$ compared with group A.

TABLE 3
Rates of Treatment-Related Complications Within 30 and 90 Days

Variable	Overall (n=106)	Patient group [n (%)]			p Value (A vs C)
		A: Elective hospitalization (n=46)	B: Other hospitalization (n=19)	C: Outpatient (n=41)	
Early complication (≤30 days)	23 (22)	10 (22)	4 (21)	9 (22)	0.981
Technique failure within 90 days	11 (10)	6 (13)	1 (5)	4 (10)	0.631
Any infectious complication within 90 days	26 (25)	14 (30)	6 (32)	6 (15)	0.080
Any complication within 90 days	40 (38)	19 (41)	8 (42)	13 (32)	0.354

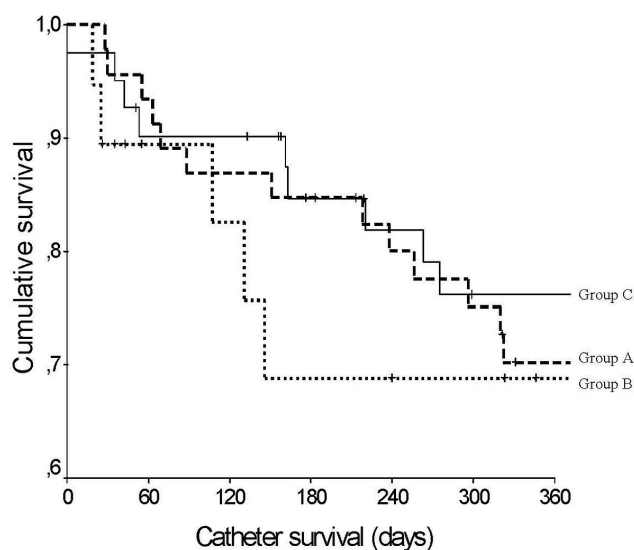


Figure 1 — Catheter survival (treatment modality survival) in the various groups during the first year. Group A = elective hospitalization; group B = other hospitalization; group C = outpatient catheter insertion. Log-rank significance: $p = 0.794$, A vs C; $p = 0.225$ (B vs C).

The total cost of the PDCI process included expenses for the preoperative outpatient visit (not incurred in electively hospitalized patients), the PDCI procedure, and postoperative monitoring and hospitalization. Table 4 shows the cost results. Average procedure-related hospitalization time was 2.67 days in the electively hospitalized patients and 0.098 days in the outpatient group. In the outpatient group, 3 patients (7%) needed immediate hospitalization for 1 – 2 days after the PDCI. Reasons for hospitalization were pain, bleeding, and perioperative bowel perforation. In 1 patient, elective hospitalization was prolonged because of postoperative pain. Average total costs were significantly higher in the electively hospitalized patients (€2320 ± €960) than in the outpatients (€1346 ± €208, $p < 0.000$).

DISCUSSION

The aims of the present study were to describe our structured PDCI protocol and to compare the results of inpatient and outpatient PDCI. Our findings suggest that

TABLE 4
Total Cost of the Peritoneal Dialysis (PD)
Catheter Insertion Process

Cost item	Cost by patient group (€)	
	A: Elective hospitalization	C: Outpatient procedure
Preoperative outpatient visit	0	119
PD catheter insertion procedure	833	833
Monitoring in recovery room	0	340
Average hospitalization (at €556/day)	1487	54
Mean total average cost	2320±959	1346±208 ^a

^a $p < 0.000$ compared with group A.

an outpatient PDCI is safe and that hospitalization is not necessary. Outcomes and complication rates were similar in electively hospitalized patients and outpatients. By reducing unnecessary admissions, considerable savings can be achieved, and the risk of nosocomial infections might be lowered. Logically, costs were lower for patients undergoing outpatient PDCI than for the hospitalized patients in the present study. Compared with an inpatient procedure, an outpatient PDCI cost 42% less (average difference: €974).

To our knowledge, the present study is the first to assess both costs and outcomes for PDCI. Numerous centers have implemented outpatient PDCI and have been using that approach for many years. However, in many countries, economic pressure on beds is less, and patients are still routinely admitted to hospital for procedures that might not require an admission. It is important that objective evidence in favor of an outpatient approach is presented so that centers who continue to take the more expensive approach can see that there is an alternative.

Several different methods of PDCI have been developed. The surgical method is still the most common technique (4). Compared with open surgery, the laparoscopic technique is slower, but produces equivalent outcomes, as reported in a UK study (5). In a recent Canadian study, radiologic catheter insertion was associated with more outpatient procedures and no excess of complications compared with the surgical method (6). In our study, open surgery and a single-cuffed catheter were used for all patients.

The mean age of our patients and the proportion with diabetes were similar to those reported in previous

studies (7–10); however, the incidences of technical failure and of peritonitis were higher (7–9,11). Recent studies have found an association of the number of PD patients with clinical outcomes. Clinic size may be a proxy for PD experience, and fewer failures tend to occur in clinics with more than 25 patients (9) or 50 patients (8) than in centers with smaller PD populations. On the other hand, the incidence of early dialysate leak has been reported to be higher in other studies (12,13).

Patients who underwent PDCI during hospitalization for other medical reasons were older and experienced higher mortality than did elective patients, reflecting a more complicated clinical setting. Otherwise, no significant differences in demographics or complications were noted between the groups. Particularly, we observed no difference in the occurrence of procedure-related early complications. Immediate postoperative complications were minor and easily resolved. Verrelli *et al.* reported similar results in their study (1).

Limitations of our study include its retrospective nature and the restricted number of patients. Comorbidities were not systematically registered. Because this was a single-center study, the results might not be generalizable. However, the demographics of patients in our study are close to those in other studies. Costs were measured as production costs for the provider. Because accounting methods differ between societies and centers, our cost analysis cannot be directly applied universally. Also, because of limited capacity in the outpatient clinic recovery room, 15 patients who were originally planned as outpatients after 2006 switched to become inpatients, and they are included in group A (elective hospitalization). Medical reasons did not affect the decision to switch. Because patients were a mix of inpatients and outpatients after 2006, selection bias might be a potential source of error. However, compared with both the inpatients before 2006 and the outpatients after 2006, the characteristics and outcomes for the 15 switched patients were similar. No statistically significant differences were observed, and we believe that this kind of non-medical selection does not constitute true bias.

CONCLUSIONS

We report the first analysis that compares both the outcomes and the costs of outpatient and inpatient PDCI. Outpatient insertion of catheters is safe, lowers demand for inpatient care, and compared with an inpatient procedure, results in similar outcomes at lower cost.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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