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Dialysis initiation and clinical outcomes in chronic kidney disease: Role of education and biomarkers

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Stockholm 2016

Published by Karolinska Institutet.
Printed by E-Print AB 2016

ISBN 978-91-7676-498-5

ABSTRACT

For patients with chronic kidney disease (CKD) who develop kidney failure, renal replacement therapy (RRT) with kidney transplantation is the best treatment option. But if this is not possible due to lack of organs or medical factors, dialysis initiation with haemodialysis (HD) or peritoneal dialysis (PD) is required. Unplanned start (UPS) of dialysis using in-centre HD with central venous catheter (CVC) as default option is common and associates with increased mortality and lower chance of receiving PD. Educating and providing PD to UPS patients is possible and with clinical outcomes comparable to UPS with HD. As RRT patients have increased cardiovascular disease (CVD) related mortality - due to not only traditional risk factors but also non-traditional risk factors such as inflammation, oxidative stress, endothelial dysfunction and protein energy wasting – there is a need to identify biomarkers reflecting such risk factors.

This thesis consists of three studies aimed to improve the knowledge about patient education in conjunction with dialysis initiation and in particular the effect of the unplanned education programme (UPS-EP) on clinical outcomes of UPS patients, and two studies of the predictive role of two putative clinically useful biomarkers (S100A12 and pentosidine) which are components of AGE-RAGE pathway.

In **Study I** we evaluated the feasibility and impact of UPS-EP to allow modality choice in 270 patients. Patients completing UPS-EP were more likely to select PD as their preferred modality. Patient survival in patients choosing and/or receiving PD was similar to HD despite age and comorbidity disadvantages of the PD patients.

In **Study II**, factors influencing three key steps in the UPS patient educational pathway: (1) referral to and receiving UPS-EP, (2) making decision on dialysis modality, (3) receiving preferred dialysis modality after decision making were analyzed. Older age reduced probability of receiving UPS-EP but not the chance of making modality decision. Cultural country factors had strong influence on probability of receiving education and making modality decision.

In **Study III** we compared UPS patients commencing dialysis with PD catheter or CVC, described characteristics of patients switching modality, evaluated patient outcomes such as PD technique failure and investigated predictors of permanent vascular access formation and clinical outcomes of patients undergoing HD during follow up. Older patients and those with congestive heart failure had lower chances receive arteriovenous fistula (AVF). Patients with AVF had better 1-year survival than those remaining on CVC.

In **Study IV** we investigated circulating S100A12 and soluble RAGE (sRAGE) in relation to peripheral or cerebrovascular disease (PCVD), inflammation, nutritional status, and mortality risk in PD patients. Plasma S100A12 and sRAGE were markedly elevated and sRAGE was inversely related to body mass indices while S100A12 associated with increased inflammation, PCVD, and mortality, suggesting that S100A12 may identify PD patients at high risk for vascular disease and increased mortality.

In **Study V** we evaluated factors linked to increased plasma pentosidine and associations with mortality in patients with different stages and treatment of CKD. Plasma pentosidine was markedly elevated and associated with low GFR, oxidative stress and inflammation, and it predicted all-cause and CVD mortality. Despite exposure to glucose containing dialysis fluids in PD patients, their plasma pentosidine concentrations were not higher than in HD patients indicating that other factors than glucose exposure matters.

LIST OF PUBLICATIONS

1. **Machowska A**, Mark Dominik Alscher, Satyanarayana Reddy Vanga, Michael Koch, Michael Aarup, Abdul Rashid Qureshi, Bengt Lindholm and Peter Rutherford. Offering Patients Therapy Options in Unplanned Start (OPTiONS): implementation of an educational program is feasible and effective. Re-submitted to BMC Nephrol.

2. **Machowska A**, Mark Dominik Alscher, Satyanarayana Reddy Vanga, Michael Koch, Michael Aarup, Abdul Rashid Qureshi, Bengt Lindholm and Peter Rutherford. Factors influencing access to education, decision making and receiving preferred dialysis modality in unplanned start dialysis patients. Patient Preference and Adherence 2016:10 2229–2237.

3. **Machowska A**, Mark Dominik Alscher, Satyanarayana Reddy Vanga, Michael Koch, Michael Aarup, Abdul Rashid Qureshi, Bengt Lindholm and Peter Rutherford. Dialysis access, infections and hospitalizations in unplanned dialysis start patients - results from the OPTiONS study. Manuscript to be submitted.

4. Isoyama N, **Machowska A**, Qureshi AR, Yamamoto T, Anderstam B, Heimburger O, Barany P, Stenvinkel P, Lindholm B. Elevated circulating S100A12 associates with vascular disease and worse clinical outcome in peritoneal dialysis patients. Perit Dial Int. 2016 5-6;36(3):269-276

5. **Machowska A**, Jia Sun, Abdul Rashid Qureshi, Naohito Isoyama, Paul Leurs, Björn Anderstam, Olof Heimburger, Peter Barany, Peter Stenvinkel and Bengt Lindholm. Plasma pentosidine and its association with mortality in patients with chronic kidney disease. PLoS One. 2016 Oct 4;11(10):e0163826

CONTENTS

LIST OF ABBREVIATIONS

AGEs	Advanced glycated end products
APD	Automated peritoneal dialysis
AVF	Arteriovenous fistula
BMI	Body mass index
CAPD	Continuous ambulatory peritoneal dialysis
CHF	Congestive heart failure
CKD	Chronic kidney disease
CVC	Central venous catheter
CVD	Cardiovascular disease
CRP	C-reactive protein
DM	Diabetes mellitus
ELISA	Enzyme-linked immunosorbent assay
ESRD	End stage renal disease
GFR	Glomerular filtration rate
HD	Hemodialysis
ICAM-1	Intercellular adhesion molecule
IL-6	Interleukin 6
MIA	Malnutrition, Inflammation and Atherosclerosis
MIMICK-1	Mapping of inflammation markers in chronic kidney disease-1 (study in prevalent hemodialysis patients)

MIMICK-2	Mapping of inflammation markers in chronic kidney disease-2 (study in prevalent peritoneal dialysis patients)
8-OhDG	8-hydroxy-2'-deoxyguanosine
PCVD	Peripheral or cerebrovascular disease
PD	Peritoneal dialysis
PEW	Protein-energy wasting
RAGE	Receptor of advanced glycated end products
ROC	Receiver operator characteristics
RRT	Renal replacement therapy
SGA	Subjective global assessment
EN-RAGE	Extracellular newly identified receptor for advanced glycated end products binding protein (also known as S100A12)
USRDS	United Stated Renal Data System
VCAM-1	Vascular cell adhesion molecule-1

THESIS SUMMARY

People who develop terminal kidney failure need to undergo renal replacement therapy (RRT). Kidney transplantation is recognised as the best treatment option but may not be possible due to lack of organs or because of advanced age and comorbidity and patients who cannot be transplanted need to choose between the two dialysis modalities, haemodialysis (HD) and peritoneal dialysis (PD). Despite advancements in dialysis technique and peri-dialysis care, still up to 50% of patients commence dialysis in an unplanned way which associates with poor clinical outcomes and lower chance to select home dialysis as the preferred dialysis modality which may lead to higher utilisation of healthcare resources. Regardless of dialysis modality, patients receiving RRT have high mortality with cardiovascular (CVD) disease as the major cause of death, which cannot be solely explained by traditional risk factors. As non-traditional risk factors typical for the state of uraemia such as inflammation, oxidative stress, endothelial dysfunction and protein energy wasting also play a pivotal role, there is a need to identify biomarkers that reflect such risk factors in this particular patient population. The current thesis consists of five studies that aimed to contribute to the current knowledge about patient education in conjunction with dialysis initiation and the predictive role of putative clinically useful biomarkers.

In studies 1-3 we evaluated how patients starting unplanned dialysis can be supported to make an informed choice between starting on HD and PD, and found that it is feasible to provide a structured educational programme to the majority of unplanned start patients allowing many of them to make a decision about their preferred dialysis treatment option. However, not all patients receive their preferred modality which may be related to country specific settings or logistic challenges and other factors that require further investigation. These studies show that it is worthwhile to educate patients who commence unplanned dialysis and that this may favour selection of PD as initial dialysis modality which may have medical and cost benefits.

In studies 4 and 5 we evaluated biomarkers S100A12 and pentosidine as predictors of patient outcomes and showed that elevated plasma concentrations of S100A12 and pentosidine are associated with increased all-cause mortality and for pentosidine also with increased CVD-mortality. These biomarkers may add value to the prognostic information or as putative targets for interventions aiming at improving patient clinical outcomes.

1. INTRODUCTION

1.1 CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is emerging as an important public health problem and a global concern for healthcare systems. The prevalence of CKD has reached epidemic proportions with 10%–12% of the population and 50% of elderly showing signs of kidney dysfunction, a condition associated with high morbidity and mortality (1). According to Kidney Disease Improving Global Outcomes (KDIGO) guidelines, CKD is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health (2) and can be divided into five stages assessed by glomerular filtration rate (GFR). CKD is usually characterized by a progressive course of worsening renal function eventually leading to the last stage, CKD 5, also called end-stage renal disease (ESRD), when GFR falls below 15 ml/min per 1.73 m^2 and the patient may require renal replacement therapy (RRT) to survive. Several RRT modalities are available for the treatment of ESRD; most patients will be treated using renal transplantation or dialysis while some patients may be managed conservatively (3).

1.2 RENAL REPLACEMENT THERAPY

Although successful kidney transplantation is by far the best treatment option in regards to survival, health-related quality of life (HRQOL) and costs saving, the lack of available donor organs, increasing patient age, burden of comorbid conditions and patient choice precludes transplantation in many ESRD patients. As a result chronic dialysis, either with peritoneal dialysis (PD) which utilizes the peritoneal membrane as a dialysis filter, or with haemodialysis (HD) entailing extracorporeal cleansing of blood, is very often the only available option for ESRD patients.

1.3 CLINICAL OUTCOMES OF PATIENTS ON PERITONEAL DIALYSIS AND HAEMODIALYSIS

Peritoneal dialysis (PD) and haemodialysis (HD) are complementary therapies sustaining survival in patients with ESRD. Clinical outcomes associated with both modalities should be considered during the dialysis decision-making process, since a difference in survival would influence the use of the two modalities. The difference in mortality seen in observational studies

with PD compared to HD has been widely debated for many years. An initial survival advantage of PD therapy was observed in Danish patients within the first 2 years of dialysis (4). NECOSAD (Netherlands Cooperative Study on The Adequacy of Dialysis) showed that the relative survival benefit of PD compared with HD among participants decreased over time (5). This finding was supported by another study from The Netherlands (6) showing that the relative mortality risk of PD patients compared with HD patients increased over time (survival benefit of PD diminished). Data from the Australian and New Zealand registry also showed lower mortality risk among patients who were treated with PD during the first 12 months (7). In the US, the survival difference between PD and HD was consistent with the data from Australia (8). More recent data from the US showed no significant difference in the risk of death for HD and PD patients during 5-year follow-up, and that the survival for PD patients is improving (9). Data from Canada also show similar outcomes with the two techniques (10).

Although the findings have not always been entirely consistent (11) most data show survival advantage of PD treatment during the first year(s) of therapy. Therefore, "integrative care" approaches; in which patients commence dialysis with PD and then are transferred to HD - when mortality risk increases - seem to be beneficial from the perspectives of both the patient and the healthcare providers.

1.4 DIALYSIS INITIATION

The optimal time of dialysis initiation has been disputed since 1980s'when Bonomini et al (12) from Bologna, Italy, reported that earlier initiation of dialysis could convey increased patient survival. In CKD patients the risk of all-cause and cardiovascular mortality increases with decline in renal function, especially when the glomerular filtration rate (GFR) decreases below 60 mL/minute (13). As patients with CKD are more likely to die than progress to renal replacement therapy, (14) it is natural to ask whether the high mortality risk in patients with CKD stages 4 to 5 can be reduced by earlier dialysis initiation. On the other hand, if the dialysis procedure is associated with factors leading to increased risk of morbidity and mortality (15) what is the added risk by starting dialysis earlier rather than later: would in fact earlier dialysis initiation instead increase the mortality risk?

Several observational studies had been performed to investigate the clinical outcomes of patients starting dialysis at various levels of estimated GFR (eGFR) showing that early start of dialysis

especially when using in centre-haemodialysis (HD) as initial therapy potentially could be harmful and also questioned the trend to early dialysis initiation based solely on eGFR; the clinical status of the patients, besides eGFR levels, should also be taken into account in the decision making process. These studies showed that the outcome after dialysis initiation was not only affected by GFR and patient characteristics but also appeared to associate with the type of dialysis (16-22).

There are many reasons why PD could be advantageous as initial dialysis therapy: better initial patient survival, preservation of vascular access sites, and higher haemoglobin and less EPO use, and better preservation of residual renal function compared to in-centre HD (23).

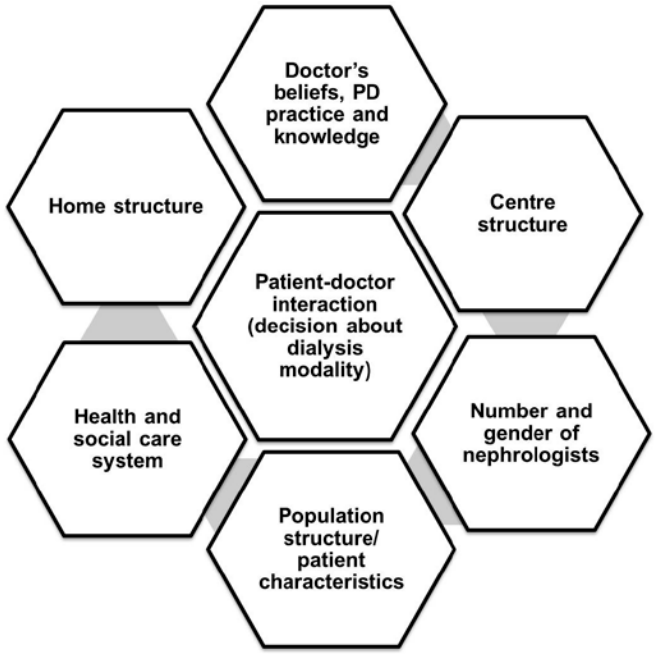
There is a continuously increasing interest in using PD also for patients commencing dialysis in unplanned, acute settings. The "PD First Strategy" is considered a suitable option for those patients as clinical outcomes of urgent PD are comparable with urgent HD start (24).

1.4.1 Factors influencing dialysis modality choice

Dialysis modality selection and distribution is of fundamental importance for patients and healthcare providers. The decision about modality selection must be influenced by a wide range of factors not related to the clinical evidence since the utilization of home therapy varies widely worldwide. According to the United States Renal Data System (USRDS), the rate of PD varies from 1.7% in Bangladesh to 74.1% in Hong Kong (25). This large difference cannot be motivated by any of the published global clinical evidence (4-10). Furthermore, registry data (25) show similarities in the incident dialysis population between comparable countries with no clear evidence that there are major age or comorbidity differences at dialysis start capable of explaining the differential use of the two modalities. In a review of secondary data from European Observatory and also data on population and demographics published by Eurostat and the World Health Organization (WHO) (26), we described several factors as main driving forces towards PD utilization disparities by affecting patient-doctor interaction and therefore decision process, such as healthcare system organization, socioeconomic factors and personal preferences of patients and health care professionals. These influential factors are presented as a theoretical construct in **Figure 1**. Considering all the factors, it was proposed that centre-specific differences within a country involving individual nephrologists' attitudes, beliefs, PD knowledge and practice organization and/or infrastructure, had a strong influence on PD use.

Careful clinical management is crucial and several factors such as early referral to nephrologist, better coordination of medical care, management of CKD complications, and education around dialysis options that is based on informed consent may contribute not only to better clinical outcomes of RRT and but also decrease the probability of unplanned start (UPS) dialysis and increase the number of patients choosing home dialysis therapy.

Figure 1. Factors that may influence PD use in Europe. All factors are changing over time and need to be considered by all stakeholders in considering current and future service provision (26).



1.4.2 Unplanned dialysis start

Unplanned start (UPS) of dialysis remains a worldwide concern and it is estimated that 24-49% of patients commence dialysis in such a way (27). UPS patients have more clinical problems such as increased morbidity and mortality (28), require increased use of healthcare resources (e.g. hospital days) (29), are less likely to receive a choice of dialysis modality and choose a home dialysis therapy, and typically start more often on in-centre HD compared with patients starting planned dialysis (30). Much of the problems related to UPS is access driven; patients starting with a central venous catheter (CVC) have much higher mortality risk as compared with

those using PD or start HD with arteriovenous fistula (AVF) or arteriovenous grafts (AVG) (31) and have increased risk of septicaemia (32).

The definition of unplanned start (UPS) of dialysis varies which can make comparisons difficult but in most studies UPS is defined, at least in part, when first dialysis has to take place despite lack of functional AV fistula or permanent PD catheter. Recently the term "suboptimal" dialysis was proposed to define dialysis commenced as a hospital in-patient, and/or with CVC (without permanent access) (33). Other criteria for defining UPS have also been proposed:

(1) Time between referral to the nephrology unit and first dialysis with a range, defined for late referral, between 1-6 months. Late referral is not entirely synonymous with UPS; however, early referral tends to be a predictor of better coordination of medical care in pre-dialysis stage, management of CKD complications, and education around dialysis option that is based on informed consent, and may therefore decrease probability of UPS. A recent meta-analysis shows that early referral is associated with reduced mortality and hospitalization, greater uptake of PD and timely placement of permanent dialysis access (34). This is clinically important as patients who start dialysis with CVCs have increased chances of prolonged CVC use and associated complications (35).

(2) Biochemical parameters e.g. estimated glomerular filtration rate (eGFR) - defined as early (above a certain level of eGFR) or late (below that level of eGFR) start which can be misleading as it does not reflect a clinical pathway. The randomized, multicentre, controlled IDEAL study aimed to evaluate the optimal dialysis start based on eGFR (17) of early vs late initiation. There was no difference in terms of survival between these eGFR defined groups but more patients in the "late" start category had UPS with temporary access.

(3) Speed of the need for dialysis - emergent dialysis, urgent dialysis and non-urgent dialysis as defined by Ghaffari (36): Emergent start < 48 hours, urgent start > 48 hours and up to 2 weeks, whilst non-urgent start were those that were able to plan and start with their modality of choice (36).

(4) Being known or "unknown" to nephrology care. There are "known" patients that despite nephrology follow up, have UPS due to unpredictable GFR decline or care pathway failures. In addition, there is a cohort of truly "unknown" patients that present with undiagnosed CKD stage 5.

1.4.3 Educational aspects of unplanned start

The choice of initial dialysis modality should ideally be made primarily by well-informed patients. In planned start patients, education programs significantly affect the distribution of dialysis modalities, increasing the proportion of patients on PD and optimizing the pre-dialysis management process (37). European guidelines (38) state that all RRT centres should provide patients and their families with well-balanced information about the different RRT modalities by means of a structured education program and this applies also to late referred and UPS patients.

The clinical concerns remain over whether it is feasible to educate UPS patients about different modalities and whether the system of care in dialysis units can be organized to educate and deliver choice of dialysis modality. Undoubtedly, the education about dialysis options of UPS patients is a challenge for every dialysis unit and it can be perceived that such patients with intense and urgent medical needs cannot be educated or make a choice. However, the results of single centre studies show that it is possible to educate UPS patients (39) and that UPS patients can commence PD (36, 40, 41), and that unplanned PD can give similar outcomes compared to unplanned HD (24, 42).

1.5 BIOMARKERS

According to the definition proposed by National Institute of Health (NIH) a biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological process, pathogenic processes, or pharmacologic response to a therapeutic intervention".

An ideal biomarker with clinical relevance should be accurate, reproducible, and measurable at a reasonable cost. In addition, it should have strong and consistent association with outcome in different cohorts. Finally, it should be practically informative enough to guide the clinician to make clinical decisions. It should be emphasized that useful clinical biomarkers may not necessarily be risk factors per se, although they reflect the pathogenic process (43).

The usefulness of the biomarker can be estimated by its: (1) *prognostic value* as a clinical or biological characteristics that is objectively measurable and that provides the information on the likely outcome of the disease or (2) *predictive value* as a clinical or biological characteristics that provides information on the likely benefit from treatment or (3) *mechanistic value* in that it enhances our understanding of the cause-and-effect pathway.

1.5.1 Novel biomarkers for cardiovascular disease (CVD)

Cardiovascular disease is a significant cause of morbidity and mortality in patients with ESRD. Identifying and intervening against common risk factors is a priority, but traditional Framingham risk factors are poor predictors in late stage chronic kidney disease (CKD) patients (1, 43-46), suggesting that the pathophysiological mechanisms may differ compared to the general population. Therefore non-traditional risk factors such as advanced glycated end products (AGEs) which play role as significant risk factors for CVD and contribute to other long term complications are of potential great interest in CKD.

1.6 ADVANCED GLYCATED END PRODUCTS (AGEs)

AGEs are formed in the body as a result of non-enzymatic processes of covalent bonding of molecules in proteins, lipids and nucleic acids with glucose or other saccharide derivatives. The process of formation of AGEs, known as Maillard reaction, starts with the formation of early glycation products called Shiff bases and Amadori products (47) that are formed in proportion to glucose concentration (48). The early glycation products are still in equilibrium with plasma glucose, and when glucose levels fall, the early glycation products can dissociate to the native proteins. Alternatively, if glycation continues, molecular rearrangement occurs, resulting in formation of the AGEs (49). The formation of AGEs is enhanced under specific conditions such as hyperglycaemia, oxidative stress and inflammation (50). Chronic uremia is a state of increased oxidative stress, and redox imbalance accelerates the accumulation of AGEs (51). In the presence of these conditions intra- and extracellular proteins can be glycated and oxidized resulting in accumulation of AGEs in essentially all tissues and body fluids. The impairment of renal function leads to reduced disposal and increased accumulation of AGEs (52) which are also naturally formed during aging processes and in specific pathological circumstances such as diabetes (53).

AGEs formation causes pathological changes via three general mechanisms including: modification of extracellular matrix (ECM), alteration of the action of cytokines, hormones, and free radicals - through interactions with AGE-specific cell surface receptors (3) - impact on the function of intracellular proteins (50).

In the ECM, glycoxidation alters the internal structure of the proteins by cross-linking with different molecules such as lipids, collagen, laminin, elastin and vitronectin that leads to

permanent changes in matrix constitution and increases the stiffness of the vasculature. Also, the activation of the transforming growth factor (TGF)-β receptor stimulates cell growth leading to increased ECM production (54-56). The mechanisms of interactions between AGEs and receptor for AGEs (RAGE) on the endothelial cell surface that triggers intracellular signalling cascade is described below.

1.6.1 Receptor for AGEs

Monocytes and macrophages were the first cells on which a high-affinity receptor for AGE (RAGE) was identified. In these studies, the interaction of AGE-protein with mouse peritoneal macrophages, using AGE-modified bovine serum albumin was characterised (48). The RAGE was cloned and expressed for the first time by Neeper et al. (57) who indicated this receptor as a new member of the immunoglobulin superfamily (49). AGEs interact with RAGE on the endothelial cell surface, and this triggers intracellular signalling cascades resulting in stimulation of NAD(P)H oxidase, increased level of reactive oxygen species (ROS) but also in upregulation of a key target: transcription factor NF-κB. In the next step NF-κB is translocated to the nucleus where it transcribe its target genes such as endothelin-1, intracellular adhesion molecule-1 (ICAM-1), E-selectin and also pro-inflammatory cytokines like interleukin-α (IL-α), interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and RAGE itself (47). RAGE is a multi-ligand receptor which can bind not only AGEs, but also to diverse group of ligands such as S100/calgranulins, amphoterin and high-mobility group box 1 (HMGB-1) (58). Soluble RAGE (sRAGE) is shed from cellular membranes into circulation where it plays role as a decoy receptor that competitively binds circulating ligands including AGEs, thereby antagonizing intracellular RAGE signalling and alleviating pro-inflammatory effects of these ligands (59). In chronic inflammatory conditions such as CVD, sRAGE levels are low, while high levels of endogenous secretory RAGE are thought to be anti-inflammatory and protective against atherosclerotic CVD (60).

1.6.2 EN-RAGE (extracellular newly identified RAGE-binding protein), also known as S100A12

This calcium-binding protein EN-RAGE, also known as S100A12 is expressed on the surface of macrophages, lymphocytes and endothelium at sites of local inflammation where it

participates in AGE-RAGE inflammatory response (61). S100A12-RAGE interaction drives pro-inflammatory gene transcription through NF-κB activation and upregulation of adhesion molecules ICAM-1 and VCAM-1 in vascular endothelial cells and (62). It also enhances migration and activation of monocytes and increase pro-inflammatory cytokine production in macrophages (63). These mechanisms suggest the potential contribution of S100A12 to the development of atherosclerosis. In PD, the heat sterilization process of glucose-based PD fluids could lead to glucose degradation products, contributing to accelerated AGE formation and therefore over-expression of RAGE. In PD patients the plasma concentration of S100A12 is 2 to 3-fold higher compared to healthy subjects and associates with carotid atherosclerosis (64). The association between high level of S100A12 and mortality was described in CKD stage 5 patients starting on dialysis (65), prevalent HD patients (66) and also in prevalent PD patients (67).

1.6.3 Pentosidine

Pentosidine is a well-characterized, fluorescent AGE structure, described for the first time by Sell and Monnier in 1989 (68). Pentosidine formation is caused by the highly reactive carbonyl compound 3-deoxyglucosone that links with the amino groups of proteins. In the circulation of uremic patients, pentosidine accumulates as both free and albumin-linked form (69). Kidneys play a key role in excretion of AGEs. The results of a study in a rat model suggest that free pentosidine (and possibly other AGEs) is filtered through renal glomeruli, reabsorbed in the proximal tubule where it is degraded or modified, and eventually excreted in the urine (70). Therefore, it is expected that the level of AGEs increases with the decline of renal function. Studies in PD patients showed that loss of residual renal function (RRF) is associated with increased plasma pentosidine and advanced oxidized protein products (AOPP), showing the beneficial role of RRF in reducing oxidative and carbonyl stress (71). Associations between pentosidine levels, biomarkers related to inflammation, malnutrition, CVD and clinical outcomes have been investigated in multiple studies. In CKD stage 5 patients investigated before starting dialysis, plasma pentosidine associates with inflammation and malnutrition (72). Circulating pentosidine associates with progression of atherosclerosis indicated by changes in carotid intima-media thickness during the first year of PD and HD therapy (73). HD patients with higher plasma pentosidine had increased risk for cardiovascular events (74), accelerated

rate of progression of aortic stiffness (75) and exhibited negative association with carotid dispensability suggesting its role in the development of arterial stiffness (76). However, other studies showed no relationship between plasma pentosidine, intima media thickness and the number of atherosclerotic plaques (77). The contribution of pentosidine to the development of cardiovascular events and mortality in CKD patients is still disputed (78) and traditional risk factors in ESRD patients have been reported to be more important for cardiovascular outcomes than elevated levels of AGEs (79).

2. AIMS

Overall aim

The overall aim of the investigations summarized in this thesis is to present the role and impact of unplanned start education programme on the clinical outcome of patients commencing dialysis in unplanned manner and also to evaluate the prognostic role of biomarkers related to AGE-RAGE pathway and its association with cardiovascular disease and mortality.

Specific aims

Paper I. To investigate the feasibility and impact of the unplanned start education programme (UPS-EP) on the dialysis modality choice in patients commencing dialysis in unplanned manner.

Paper II. To investigate the factors that may influence receiving education, decision making process and enacting on the dialysis modality decision made by unplanned start patients.

Paper III. To evaluate the impact of the initial dialysis access on patient clinical outcomes and its relation with hospitalization, dialysis related procedures and infections.

Paper IV. To study the association between circulating S100A12 (EN-RAGE, extracellular newly identified receptor for advanced glycated end products binding protein) and presence of cardiovascular disease (CVD) and mortality in PD patients.

Paper V. To compare the level of pentosidine in CKD patients with different stages of CKD and to investigate the prognostic role of pentosidine in CVD and all-cause mortality.

3. PATIENTS AND METHODS

The work presented in this thesis is based on five observational cohorts. In **study I, II** and **III** we used the data from Offering Patient Therapy Options in Unplanned Start (OPTiONS) study. In **study IV** we used material from Mapping of Inflammation Markers in Chronic Kidney Disease 1 (MIMICK-1; prevalent HD patients) and Mapping of Inflammation Markers in Chronic Kidney Disease 2 (MIMICK-2; prevalent PD patients) cohorts. In **study V** we used material from MIMICK-1 and MIMICK-2 cohorts, and from cohorts of patients with CKD stage 5 initiating dialysis (Malnutrition, Inflammation and Atherosclerosis, MIA) and patients with CKD stage 3-4 (PRIMA) respectively as well as community-dwelling control subjects.

3.1. PATIENTS AND METHODS IN STUDY I, II AND STUDY III

3.1.1 Offering Patients Therapy Option in Unplanned start (OPTiONS)

This was a non-interventional, multi-centre, observational study of 270 unplanned start (UPS) patients, who were followed up for 12 months. Twenty-six centres in six European countries (Austria, Denmark, Germany, France, Sweden and United Kingdom) agreed to recruit all UPS patients presenting in their units. In these centres, all UPS patients were identified on clinical presentation and considered actively for education within the structured unplanned start education programme (UPS-EP) with the use of decision support tools. UPS patients who were judged clinically to not be suitable for this educational approach or who would not be able to make a modality choice for medical reasons were still identified and included in the overall UPS cohort. Patients could receive the UPS-EP at the time of presentation or following dialysis start. The study inclusion criteria were CKD stage-5, age between 18 and 90 years at the time when informed consent was signed, and dialysis commenced in an unplanned way on the basis of clinical criteria of presentation to the nephrologist within one month of needing dialysis (as ‘unknown” patient) AND/OR being followed by nephrologist but requiring urgent dialysis commencement by central venous catheter (CVC) or an acutely placed PD catheter. The exclusion criteria included: diagnosis of acute kidney injury (AKI) rather than CKD stage 5 as defined by NICE Guideline (80); clinical decision to actively follow a conservative clinical management plan (chronic dialysis not planned); and, other serious or acute conditions that, in the investigator’s opinion, would preclude participation in the study or where life expectancy

was estimated at 6 months or less. Patients gave informed consent for inclusion and data collection at the time of UPS presentation or in the recovery phase around the time of hospital discharge. The ethics approval were granted by all appropriate ethics committees: Regionala etikprövningsnämnden i Stockholm (EPN), 2012/2:2; West Midlands MREC, UK 11/WM0160; Ethikkomission der Atrzekammer Nordrhein, 2011222; Ethikkomission der Atrzekammer Saarlandes, 127/11; Ethikkomission Tubingen, 376/2011B02; Ethikkomission der Atrzekammer, Stuttgart 1816/BX; Ethikkomission der Bayerischen, Munich 11068; Ethikkomission der Medizinischen Universitat Wien, Vienna 605/2011; CNIL, Paris EGY/ABE/AR122444; CNOM, Paris FR/IH/SRMI/CN-11-349-117; CCTIRS, Paris 11.688.

3.1.2 Unplanned start education programme (UPS-EP)

The UPS-EP was developed in an attempt to modulate the UPS patients' pathway and allow dialysis modality education and modality decision making by UPS patients. The program is composed of an education program, together with an examination and optimization of the flow of UPS patients in renal care units. The program was developed in collaboration with five European dialysis units linked to academic institutions specialized in patient education. The program is focused on facilitating the decision making process for patients choosing chronic RRT. Thus, the UPS-EP material included information on HD, PD, home HD and conservative care as well as transplantation. The UPS-EP was delivered to the patients during at least three individual sessions by nurses using motivational interviewing methodology, at a pace determined by the educational nurse with assessment of the clinical condition. Supporting materials included a dialysis options booklet matching the educational material delivered by the nurse, a photograph based book showing PD, HD and home HD, and a unit-specific video of the techniques alongside visits to the HD unit and demonstration of PD. In addition, decision support tools were used as key elements of UPS-EP whereas their use in CKD education at the time of commencement of OPTiONS was minimal. Decision aids (decision support tools) present a detailed, specific and personalized picture of options and outcomes to prepare people for decision making. They differ from health education materials, which tend to be broader in perspective (helping people to understand diagnosis, treatment, and management but not assisting with a specific personal choice between options). Three aids were available to centres with the educators choosing for the individual patient from the Ottawa online decision aid, a

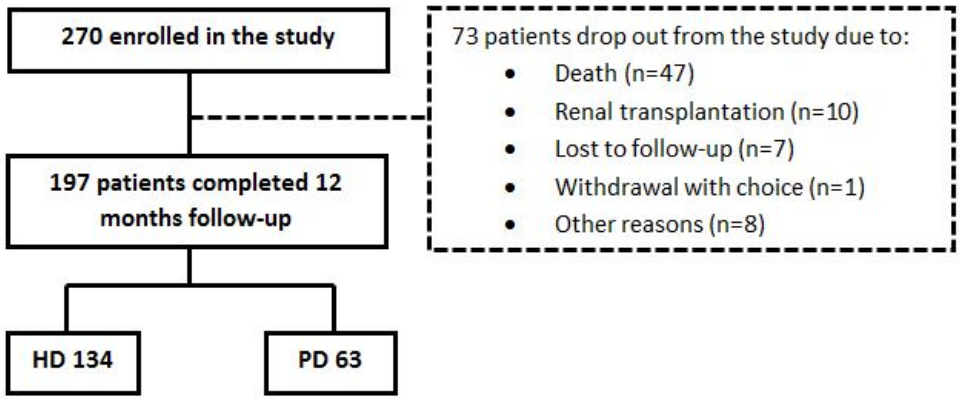
self-completion balance scale and a set of decision cards which allowed the patient to prioritize the value to them of specific issues and factors related to dialysis modalities.

The UPS-EP also consists of analysis of UPS patient flow in a dialysis unit with process improvement approach to understand and resolve issues - the units mapped out their unplanned start pathway to understand and improve specific bottlenecks and constraints. The aim was to improve the pathway to patient education, decision making and formation of permanent access (AV fistula or peritoneal catheter).

3.1.3 Data collection

Demographic or clinical data were collected either from the patients' healthcare records or from routine patient-health care professional interactions at baseline, 6 months and 12 months. This included patient demographics, medical history including comorbidities assessed by Charlson comorbidity index (CCI), dialysis access procedures, details of the presentation with end-stage renal failure requiring UPS and details of starting modality, access interventions and the number and length of hospitalization linked to UPS. Data collection at 6 months (defined as 6 months following first HD session or first PD day at home if PD from the start of dialysis) and 12 months (defined as 12 months following first HD session or first PD day at home if PD from the start of dialysis) recorded patient status, dialysis modality, and if, when changed, details of dialysis access procedures, brief details of dialysis related infectious events and number and length of any hospitalizations. The patients flow throughout the study is presented in **Figure 3.1**.

Figure 3.1 The flow of UPS patients during the study follow up time.



3.1.4 Peritonitis and bacteraemia rate

In **studies I and III** peritonitis rate was calculated according to ISPD guidelines (81) and expressed as months of PD at risk, divided by number of episodes, and expressed as interval in months between episodes and also as number of infections for a time period, divided by dialysis-years' time at risk, and expressed as episodes per year.

In order to compare the severity of the infection events we applied the same calculation scheme to show the bacteraemia rate among HD patients calculated based on the number of haemodialysis bloodstream infection. In our study, the definitions are classified according to the KDIGO Vascular Access guidelines (82). Bloodstream infection was defined as blood culture results positive for the presence of bacteria with or without the accompanying symptom or fever.

3.1.5 Hospitalization, procedures and infections

In **study III** we calculated the cumulative incidence of dialysis access related procedures and hospitalization (admissions and length of time), the number of dialysis access related infections such as PD tunnel infection, PD exit site infection, peritonitis, HD tunnel infection, HD exit site infection, HD bloodstream events during the study period. The access related procedures were also categorized 4 groups according to the number of procedures: 0, 1-2, 3-4 or ≥5 procedures.

3.1.6 Statistical analysis

In **studies I, II and III** data are expressed as median (10th to 90th percentile), percentage, odds or hazard ratio (95% CI, confidence intervals), as appropriate. Statistical significance was set at

the level of $p<0.05$. For comparison between two groups non –parametric Wilcoxon test was used - and for three or more groups - non-parametric Kruskal-Wallis ANOVA test was used. Chi-square test was used for nominal variables. Kaplan Meier technique was used to calculate crude one-year patient and techniques survival. Statistical analyses were performed using statistical software SAS version 9.4 (SAS Campus Drive, Cary, NC, USA).

In **study I** multivariate logistic regression was performed to determine factors predicting if patients would be receiving PD vs HD dialysis therapy during the study, including initial dialysis modality. Explanatory variables in the model include age, gender, eGFR, presence of diabetes, hospitalization for unplanned start, time between first referral to nephrologists and first dialysis session and received education.

In **study II** multivariate logistic regression was performed to investigate the factors that may influence the key 3 steps in the education pathway: (1) receiving education, (2) making dialysis modality choice, and (3) receiving modality according to patient preferences. Depending on the model the following explanatory variables were included: age, gender, presence of diabetes, congestive heart failure (CHF), time between first referral to nephrologists and first dialysis session (categorized as needing dialysis at the referral day, or later), initial dialysis modality (modality to which patient was assigned by the physician), and center (countries were divided to two groups based on historical home dialysis use: France (FR), Germany (DE), and Austria (AU), and United Kingdom (UK), Sweden (SE), and Denmark (DK) respectively), and patient source (in-patient/out-patient admission as a proxy for timing of the education).

In **study III** multivariate logistic regression was performed to investigate the factors that may predict presence of fistula. Explanatory variables included were: age, gender, received UPS-EP, presence of diabetes (DM) and presence of congestive heart failure (CHF). Multivariate Cox regression analysis adjusted for type of vascular access, age, sex, country and presence of CHF was performed to investigate one-year, all-cause mortality in patients who remained on haemodialysis therapy during whole period of the study (n=158). We estimated the crude one-year technique failure in PD patients (n=72) using Kaplan-Meier technique, defining transfer to HD therapy as technique failure.

3.2 PATIENTS INCLUDED IN STUDY IV

3.2.1 Mapping of Inflammation Markers in Chronic Kidney Disease 1 (MIMICK-1)

The MIMICK-1 cohort comprises prevalent HD patients from six HD units in the Stockholm-Uppsala region as described previously (83). This study originally aimed at monitoring inflammatory markers in prevalent HD patients. The recruitment of patients took place from October 2003 until March 2004. The inclusion criteria were more than three months on dialysis, and age >18 years. Exclusion criteria covered unwillingness to participate or infections such as human immunodeficiency virus (HIV) or methicillin-resistant Staphylococcus aureus (MRSA). In **study IV** we included 190 patients (106 men, median age of 67 years) from the MIMICK-1 cohort with available measurements of S100A12 and sRAGE. The Ethics Committee of the Karolinska Institutet, Sweden, approved the study (Dnr.03/415).

3.2.2 Mapping of Inflammation Markers in Chronic Kidney Disease 2 (MIMICK-2)

This cohort comprises prevalent PD patients. The study primarily aimed to monitor inflammatory markers in all prevalent PD patients who were controlled at the Karolinska University Hospital at Huddinge and at Danderyd´s hospital in Stockholm who had been treated for at least three months on continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD). The description of the study was presented previously (84). Among 97 patients eligible for the study, 13 patients did not start the study due to transfer to HD, transplantation or death, and among 2 patients S100A12 and sRAGE could not be measured due to lack of serum sample. The study IV comprises 82 patients (70% of men, median age of 65 years). Peritoneal dialysis was provided as CAPD to 77 % of the patients and APD to 23 % of patients. The patients were recruited from March 2008 to April 2011. The Ethics Committee of the Karolinska Institute at the Karolinska University Hospital Huddinge, (EPN) Stockholm, Sweden, approved the study protocol and informed consent was obtained from each patient. (Dnr 03/415, Dnr 2007/166331/4).

3.2.3 Control subjects

For comparative reasons, 50 community-dwelling and thus in most cases healthy subjects (31 men, with median age of 63 years), randomly selected by Statistics Sweden (SCB, a government agency) from the region and who accepted to participate as volunteers, were included in the

analysis. In **study IV** the prevalent HD patients and control subjects underwent similar measurements as those of the prevalent PD patients. These individuals were recruited from February 2003 until April 2004. The Ethics Committee of the Karolinska Institute at the Karolinska University Hospital Huddinge, (EPN) Stockholm, Sweden, approved the study protocol and informed consent was obtained from each individual (Dnr 40/02).

3.3 PATIENTS INCLUDED IN STUDY V

3.3.1 Mapping of Inflammation Markers in Chronic Kidney Disease 2 (MIMICK-2)

The description of the study was presented previously (84) and also above. In total, 74 prevalent PD patients (median age 61 years; 64% males) were included in **study V**. The Ethics Committee of the Karolinska Institute at the Karolinska University Hospital Huddinge, (EPN) Stockholm, Sweden, approved the study protocol and informed consent was obtained from each patient (Dnr 03/415, Dnr 2007/166331/4).

3.3.2 Mapping of Inflammation Markers in Chronic Kidney Disease 1 (MIMICK-1)

The study was described previously (83) and also above. In total 195 prevalent HD patients (median age 64 years; 57% males) were included in **study V**. The Ethics Committee of the Karolinska Institute at the Karolinska University Hospital Huddinge, (EPN) Stockholm, Sweden, approved the study protocol and informed consent was obtained from each patient (Dnr.03/415)

3.3.3 MIA cohort

MIA cohort is an ongoing, prospective cohort study started in 1994 and described in more detail elsewhere (85, 86). Incident CKD stage 5 patients (GFR<15 mL/min) were evaluated close to start of dialysis (either HD or PD) at the Karolinska University Hospital at Huddinge, Sweden. Patients were followed up until death or transplantation. Patients were invited to attend an additional examination after approximately one and two years of dialysis therapy. In **study V** we included in total 386 patients, who were recruited from June 1994 until October 2012. The median age of patients was 55 years and 60% were males. The Ethics Committee of the Karolinska Institute at the Karolinska University Hospital Huddinge, (EPN) Stockholm,

Sweden, approved the study protocol and informed consent was obtained from each patient (Dnr. 273/94)

3.3.4 CKD stage 3-4

This cohort consists of 54 patients with CKD stage 3-4 recruited from the renal outpatient clinic of Karolinska University Hospital from December 2001 until March 2004. The description of the study was presented previously elsewhere (87). The median age of patients included in **study V** was 60 years, and 74% were males The Ethics Committee of the Karolinska Institute at the Karolinska University Hospital Huddinge, (EPN) Stockholm, Sweden, approved the study protocol and informed consent was obtained from each patient (Dnr 244/01)

3.3.5 CKD stage 1-2

In **study V**, 37 individuals with CKD stage 1-2 from a population based sample randomly selected by Statistics Sweden (a government agency) from the Stockholm region and who accepted to participate as volunteers were found to have signs of mild CKD (macro- or microalbuminuria or reduced GFR). These individuals were serving as controls and were included in the studies for comparative reasons for the CKD stage 3–4 patients and thus they have similar age and gender distribution as the CKD stage 3–4 patients. The median age was 68 years and 70% were males. The individuals were recruited from February 2003 until April 2004. The Ethics Committee of the Karolinska Institute at the Karolinska University Hospital Huddinge, (EPN) Stockholm, Sweden, approved the study protocol and informed consent was obtained from each individual (Dnr 40/02).

In addition, **study V** included 59 CKD patients from an ongoing study (Kärl-Tx) of vascular changes in patients undergoing living donor kidney transplant, LD-Rtx cohort. The patients in LD-Rtx cohort were allocated to the various groups in study V depending on their stage of CKD or dialysis treatment: One patient was allocated to CKD stage 3-4, 24 patients to CKD stage 5, 17 patients to HD and 18 patients to PD. The Ethics Committee of the Karolinska Institute at the Karolinska University Hospital Huddinge, (EPN) Stockholm, Sweden, approved the study protocol and informed consent was obtained from each individual (Dnr 2008/1748-31/2).

3. 4 METHODS IN STUDY IV AND STUDY V

3.4.1 Evaluation of peripheral or cerebrovascular disease among PD and HD patients

In **study IV** peripheral vascular disease defined as presence of arterial insufficiency of the extremities, carotid or renal artery stenosis, or aortic aneurysm, and cerebrovascular disease, defined as presence of stroke, transient ischemic attack, subdural hematoma, and intracerebral or sub-arachnoid haemorrhage (88) was recorded and combined into one category, peripheral vascular disease or cerebrovascular disease, or both, PVCD.

3.4.2 Blood sampling and laboratory analysis

Plasma samples were taken and stored at -70°C, if not analysed immediately. Circulating levels of albumin (bromcresol purple), total cholesterol, creatinine and high-sensitivity C-reactive protein (hsCRP) were analysed using certified methods in the Department of Clinical Chemistry, Karolinska University Hospital Huddinge. Interleukin-6 (IL-6) was measured by Immulite immunoassay Analyzer (Siemens Healthcare, Erlanger, Germany), using assays manufactured for this analyser and according to the manufacturer's instructions. The soluble form of vascular cell adhesion molecule 1 (sVCAM-1), a marker of endothelial activation, was analysed by commercial ELISA kits (R&D Systems Europe, Ltd, United Kingdom). 8-hydroxy-20-deoxyguanosine (8-OHdG) was measured using a commercial competitive enzyme-linked immunosorbent assay kit (Japan Institute for the Control of Aging, Shizuoka, Japan), following the manufacturer's instructions. Advanced oxidation protein products (AOPP) were analysed by a modified assay (84), correcting for impact of serum triglycerides to yield modified AOPP (mAOPP).

In **study IV** plasma levels of sRAGE (Human RAGE Quantikine ELISA; R&D Systems, Inc., Minneapolis, MN, USA), S100A12 (Circulex S100A12/EN-RAGE ELISA kit; Cyclex Co., Ltd., Nagano, Japan), and Nε-(Carboxymethyl) lysine (CML; Cyclex Co., Ltd., Nagano, Japan) were measured using ELISA according to protocols provided by the manufacturer.

In **study V** plasma pentosidine was analysed by reverse-phase high performance liquid chromatography (HPLC) as described previously (72). Circulating pentosidine is mainly present in protein bound form with albumin (69). Therefore, the total (free plus protein bound) plasma

pentosidine concentration, measured in nmol/L, was corrected for albumin and expressed as nmol of plasma pentosidine per gram of albumin.

3.4.3 Nutritional status

In all cohorts in **study IV** and **study V**, body mass index (BMI) was calculated as the body weight in kilograms divided by the square of patient height in meters. In addition subjective global assessment (SGA) was used to evaluate the overall protein-energy wasting (PEW) in CKD patients as described previously (89). Briefly, SGA score is based on six subjective assessments, three were based on the patient's history of weight loss, incidence of anorexia or incidence of vomiting, and three were based on subjective grading of muscle wasting, presence of oedema and loss of subcutaneous fat. Then, each patient was given a score reflecting the overall nutritional status: 1 = normal nutrition, 2 = mild PEW, 3 = moderate PEW and 4 = severe PEW. In the current study, PEW was defined as SGA score >1.

In **study IV** body composition was assessed in PD patients and controls, by dual energy x-ray absorptiometry (DEXA; Lunar Corp., Madison, WI, USA) estimating lean body mass (LBM) and fat body mass (FBM). In HD patients, FBM and LBM were assessed according to Durnin et al. (90) from biceps, triceps, subscapular, and supra-iliac skinfold thickness measurements with skinfold caliper (Cambridge Scientific Instruments, Cambridge, MD, USA); LBM (LBMI) and FBM (FBMI) indices were calculated according to Kyle et al. (91) and expressed as kg/m^2.

3.4.4 Statistical analysis

In **studies IV and V** all statistical analyses were performed using statistical software SAS version 9.4 (SAS Campus Drive, Cary, NC, USA). Statistical significance was set at the level of $p<0.05$. Comparisons between 2 groups were assessed with non-parametric Wilcoxon test for continuous variables and a $\chi 2$ test for nominal variables. Differences among three groups were analysed using nonparametric ANOVA Kruskal-Wallis test followed by Dunn's test. Non-parametric Spearman rank correlation analysis was used to evaluate the association between parameters.

In **study IV** data are expressed as mean ± standard deviation (SD) or median (range of 25 to 75th percentile) or percentage, as appropriate. Multivariate logistic regression analyses were used to assess determinants of existing PVCD with data expressed as odds ratio, OR, with 95%

confidence intervals, 95% CI. A competing risk Cox regression model was used to analyse the independent risk of 2 events—renal transplantation or death. If a patient received renal transplantation, then the outcome of mortality was censored. A Cox model with a data augmentation method was used to analyse the competing risks. The two types of events were evaluated to see if they had a constant hazard ratio. Covariates were interacted with the outcome to analyse the independent effect of covariates on each of 2 competing endpoints. The cumulative incidence of events was calculated.

In **study V** data are expressed as median (10 to 90th percentile) or percentage, or as relative risk (risk ratio), RR (95% CI, confidence intervals) as appropriate. To determine the adjusted RR for death associated with one standard deviation, 1-SD, higher pentosidine, multivariable GENMOD regression analysis was performed, see http://support.sas.com. Age, gender, diabetes (DM), SGA, hsCRP, 8-OHdG and patient cohorts were included in the model. A multiple imputation of missing values was performed using the function PROC MI, with all variables in the covariate section used to produce the values for imputation. The results for each imputation were generated by using PROC MIANALYZE and GENMOD regression analysis.

Receiver operating characteristics (ROC) curves were analysed allowing calculation of areas under the curves (AUCs) and cut-off values for pentosidine in relation to all-cause and CVD-related deaths.

4 RESULTS AND DISCUSSION

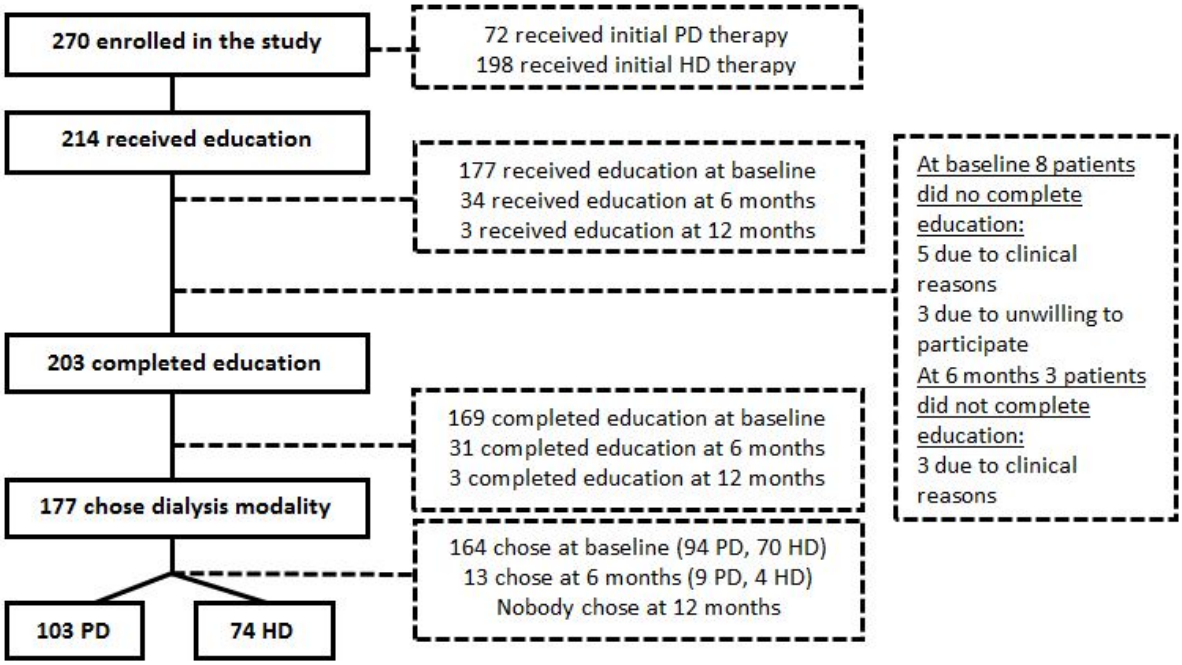
4.1 STUDY I

In this study we investigated the feasibility and impact of unplanned start educational programme (UPS-EP) intended to intervene in patient pathway and improving care of unplanned start (UPS) patients by facilitating care pathways and enabling informed choice of dialysis modality.

From 270 patients enrolled in the study, 214 patients received UPS-EP and 56 never received UPS-UP. The patients who never received UPS-EP were significantly older ($p=0.01$), more comorbid (CCI, $p<0.01$), and they were distributed differently across the countries compared to those who received UPS-EP. There was a trend regarding patient source with a higher in-patient admission in the group who never received UPS- EP ($p=0.09$).

Most of the patients (177/214) received UPS-EP immediately or shortly after UPS presentation, 34 patients within the first 6 months after commencing dialysis, and 3 patients after 12 months. Whereas 203 out of the 214 UPS-EP patients completed the educational programme, 11 patients did not complete it because of their medical condition (n=8) or unwillingness to participate (n=3). Following the completion of UPS-EP, 177 patients made a decision on initial dialysis modality, 103 patients chose PD and 74 HD, while 26 patients did not make any choice, or were unable for clinical reasons to make a decision. The flow of patients through the UPS-EP is presented in **Figure 4.1**

Figure 4.1 Flow of 270 UPS patients through UPS-EP.



The figure describes the patients flow through the education pathway. From 270 patients enrolled who all had been initiated on dialysis, 72 on PD and 198 on HD, 214 patients received education and 203 completed education at the different time points of the study with the majority completing it on baseline. In total, 177 patients made a decision about their preferred chronic dialysis treatment and among those 103 patients chose PD and 74 chose HD

The results of multivariate logistic regression analysis showed that having diabetes: OR= 1.88 (CI, 1.05 – 3.37) and receiving UPS-EP: OR= 4.74 (CI, 2.05 – 10.98) were statistically significant predictors of receiving PD.

From 177 patients who completed UPS-EP, 103 patients declared that they would choose PD and 74 patients that they would choose HD. Patients who chose PD were more comorbid (CCI, $p=0.01$), with higher prevalence of congestive heart failure ($p<0.01$), were distributed differently across countries ($p<0.01$) and with trend towards higher number of in-patient admissions ($p=0.05$) than in the patients choosing HD.

Among the investigated UPS patients not everyone received the modality they selected after education. In our study, 89 patients chose and received PD and 70 patients chose and received HD according to their recorded decision. PD patients were significantly more comorbid (CCI, $p=0.02$), had more often medical history of congestive heart failure ($p<0.001$) and myocardial

infarction (p=0.02), were significantly more often from in-patient UPS admission (p=0.02) or referred from primary care (p=0.04), and were differently distributed among participating countries (p<0.001).
Since not all the patients received their preferred therapy we compared patients who completed the UPS-EP according to the modality that they actually received.

The results show that compared to those treated by HD, those treated by PD were significantly more comorbid (CCI, p=0.04), with higher prevalence of congestive heart failure (p<0.01) and, were significantly more often from in-patient admission (p=0.02), and referred from primary care (p=0.02), and were differently distributed among participating countries (p<0.001).

Using Kaplan-Meier analysis we found no significant difference in one-year survival between patients who chose and received PD (n=89) and HD (n=70) and also there was no significant difference between patients who were actually treated with PD (n=93) and HD (n=84) respectively.

The overall peritonitis rates in PD patients were lower than ISPD recommended goals (81).

In study I we showed that it is feasible to provide a programme like UPS-EP to patients starting UPS dialysis; most patients were able to commence (79%) and complete education (75%). We confirmed the results of single centre studies (40, 41) showing that it is possible to commence UPS dialysis with PD. The OPTiONS study employed decision support tools which were shown to facilitate the decision making process by patients (92) and this helped the majority of patients to complete education and make a decision (66%) about their treatment option.

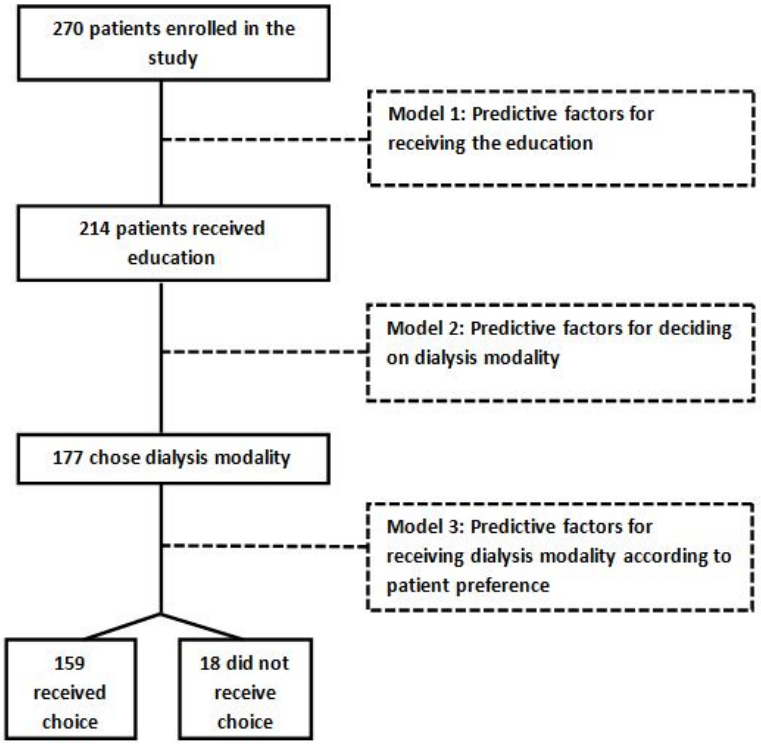
Receiving UPS-EP education was a significant predictor of receiving PD in the logistic regression model. After making a decision, 103/177 patients - regardless of comorbidity disadvantages - selected PD. These results demonstrate that PD was not being selected only by younger and fitter patients and that a wide range of patients were receiving education and choosing PD.

It is noteworthy that throughout the study patients choosing and receiving PD and also those selecting and in fact being treated with PD were significantly more comorbid compared to their HD counterparts. Nevertheless, overall patient survival was the same in patients choosing and/or receiving PD compared to those treated by HD despite the age and comorbidity disadvantages in those treated by PD. Noteworthy, OPTiONS study was not powered to measure survival as a primary outcome measure and only one year follow up was performed; nevertheless, there are no indications that patients´ choice of modality associated with poor clinical outcomes in UPS patients.

4.2 STUDY II

In this study we investigated factors that may influence three key steps in the patient UPS-EP education within the OPTiONS study: (1) referral to and receiving UPS education, (2) making a decision about dialysis modality, (3) receiving the preferred dialysis modality after decision making (**Figure 4.2**).

Figure 4.2 Patients flow through the education pathway and application of regression models which have been developed to understand possible factors influencing the 3 key steps of the UPS-EP education pathway: receiving UPS-EP, decision making and enacting choice.



We presented that patients who were older than 69 years had 60% lower chances of receiving education, OR=0.40 (CI, 0.20 – 0.80). Odds for receiving education were significantly higher among patients with PD as an initial dialysis modality, OR=4.81 (CI, 1.85 – 12.50). Also country was a significant predictor of receiving education, patients in Germany (DE), France (FR) and Austria (AU) had markedly lower chances of receiving education compared to patients from United Kingdom (UK), Sweden (SE) and Denmark (DK): OR = 0.38 (CI, 0.18 – 0.82).

We showed that patients starting on PD as an initial dialysis modality OR=6.33 (CI, 2.89 – 13.87) had significantly higher chances of making a decision about dialysis modality. Also country category was shown to be statistically significant predictors of decisions about dialysis modality: patients from DE, FR and AU had smaller chances of making a choice than patients from UK, SE and DK, OR=0.50 (0.28 – 0.87)

Regardless of the ability to make a dialysis modality decision after receiving education, there were still patients who did not receive the dialysis option according to their informed choice. We presented that while factors such as age, gender and DM failed to reach statistical significance as predictors for patients to receive their preferred option for initial dialysis modality, the only significant predictor was history of myocardial infarction, OR=0.15 (CI, 0.05 – 0.48). Thus, patients with myocardial infarction were less likely to receive their preferred choice of final modality.

We also performed a simple analysis of annual dialysis costs to assess the potential economic impact of UPS-EP which demonstrated potential cost savings of implementing the dialysis choice made by the UPS patients through UPS-EP.

The majority of patients were able to receive UPS-EP. In our study the elderly patients were less likely to be referred for education. Also country factor and initial PD dialysis access were significant predictors of the referral to education.

Regardless our findings, we believe that age should not be considered as contraindication for providing education and offering modality choice. Previous studies showed that elderly patients (93) have good clinical outcomes with PD and that age is not a barrier to choice of PD.

The variability in PD usage between various parts of Europe is well known (26) and appears to reflect physician belief and practice patterns which are also playing out within the context of the current study. Our observation that initial dialysis access is a predictor of receiving education can reflect that physicians who firmly believe in patient choice of home dialysis with PD and support their willingness to commence PD are more likely to educate patients.

The benefits of decision support tools in terms of improving knowledge and reducing decisional conflicts have been summarized in a recent systematic review (94). The OPTiONS study aimed to facilitate the decision making process by using decision support tools as a part
of the programme. In the current study, age and comorbidity were not influential factors on decisions about dialysis modality. Thus these factors should not be used as part of value

judgements by clinical teams to assume which patients can or cannot make decisions; with the correct information and decision support, decision making is possible. Similar to the previous model, factors related to the country and the initial dialysis modality, were significant. Those findings emphasize again the difference in overall acceptance of patient centricity of physicians in clinical practice across Europe.

The problem remains on the final step of the educational pathway, as the proposed model failed to identify significant factors influencing the enactment of patient preferred choice. Therefore, we suggest that pathway of care or logistic challenges which require further examination - in order to employ further interventions in clinical practice following patient education and decision making to ensure modality choice progresses - need to be identified and improved.

4.3 STUDY III

In the **study III** we aimed to examine firstly the putative differences in patients commencing unplanned dialysis with PD catheter or CVC as the starting access. Secondly, we examine the patients who switched the modality during the study including PD technique failure and HD to PD transfers to examine the overall patient pathway impact. Finally, we also investigate the predictors of permanent vascular access formation and clinical outcomes of patients undergoing only HD.

Patients starting dialysis with PD catheter (n=72) were significantly older (p=0.02), had more comorbid conditions (CCI, p=0.001) with higher prevalence of diabetes (p=0.01), congestive heart failure (p<0.001) and myocardial infarction (p<0.01) and also had significantly different aetiology of CKD (p=0.001) compared to patients starting with CVC (n=198). The majority of patients were referred during an in-patient admission and referred to the nephrology unit from other hospital specialties. Patients starting with PD catheter had significantly lower number of procedures (p<0.001) throughout the entire study and significantly more of them received UPS-EP (p=0.02) and were distributed differently across countries (p<0.001).

From 72 patients who started dialysis with initial PD, 13 switched the therapy to HD. Patients who switched the therapy had significantly higher number of hospitalization events (p<0.01) and number of procedures (p<0.001) compared to those who remained on the therapy possibly

due at least in part by the need of new dialysis access. The crude technique survival for the patients at one year was 79% with transfer to PD usually occurring in the first 90-100 days.

From 198 patients who commenced HD with CVC, 158 remained on this modality and 40 switched the therapy. Patients who switched from HD to PD required access procedures more often ($p<0.001$) and were receiving unplanned start educational programme in higher proportion ($p<0.001$) compared to those who remained on HD throughout the study. The distribution of the countries differed significantly between those two groups.

In our study, 85 patients commenced HD dialysis with CVC and remained with CVC and 73 patients had permanent access with arteriovenous fistula (AVF) or graft. Patients who during the course of the study received permanent access were significantly younger ($p<0.001$), had lower prevalence of CHF ($p<0.001$), had higher number of hospitalization events ($p<0.01$), but did not stay significantly longer in hospital ($p=0.18$), and also had higher number and different distribution of access procedures ($p<0.001$).

We showed in multivariate logistic regression analysis that age, OR= 0.34 (CI, 0.17 – 0.68), and congestive heart failure, OR= 0.31 (CI, 0.13 – 0.78), were significant predictors of receiving AV fistula: older patients had 66% lower chances of receiving AVF and patients with congestive heart failure had 69% lower chances of receiving AVF.

The results of Cox regression analysis including adjustments for access (AVF or CVC), age, sex, country and CHF showed that younger patients: HR=0.39 (95% CI, 0.16 – 0.93) who received AVF had significantly lower risk of death, HR=0.11 (95% CI, 0.03 - 0.38).
The majority of UPS patients commence dialysis with a CVC (36) and infrequently are able to transfer to PD (30) and indeed often remain dialysing with a CVC. The potential risks of long term use and CVC related complications are well-known (35). We showed that patients commencing dialysis with a PD catheter had fewer number of access procedures compared to those started with CVC, confirming this potential health system benefit. We observed no differences in regards to age and comorbidities between patients switching from PD to HD and those remaining on PD during the follow-up, confirming that PD can be a suitable modality in

these groups. Early modality switch from PD was associated with higher infection rates thus emphasizing the importance of the first 90 days in PD management (95). Interestingly, in the group who commenced HD with CVC group, 40/198 switched to PD and patients in this group were more likely to have received UPS-EP, leading us to conclude that this transfer was driven by patient choice. Similar to patients switching from PD to HD, patients switching from HD to PD were not different in terms of age or comorbidity compared to those remaining on HD during the follow-up. Therefore, there was no evidence that younger or healthier patients were preferentially transferred.

There is evidence (31) and clinical guideline recommendations (96) stressing the importance of the benefit of permanent access with AVF compared to CVC. Studies have observed the survival challenges associated with suboptimal dialysis start with CVCs (27). Throughout our study, 73/158 patients who had a reported permanent access procedure were younger and less frequently had cardiac failure compared to patients who remained on CVC. It appears that it is likely that the HD patients who never received a permanent access procedure contains a group of patients in whom the physician is actively deciding to try to maintain a CVC, particularly among older and those with cardiac failure. This is confirmed by logistic regression analysis where younger age and lack of congestive heart failure were significant factors determining the presence of permanent access, and also AVF and younger age was associated with better one-year survival.

4.4 STUDY IV

In the study IV we evaluated circulating S100A12 and sRAGE in relation to vascular disease, inflammation, nutritional status, and mortality risk in PD patients. We compared PD, HD and control individuals. Compared with the HD patients, median S100A12 was 1.9 times higher, median sRAGE lower by 14%, and median S100A12/sRAGE 2.4 times higher in PD patients. Among PD patients 25% were high or high-average (53%) transporters, while 3% were low or low-average (19%) transporters; however, plasma S100A12 and sRAGE levels were not significantly different between the transport groups.

The results from univariate analysis showed that in PD, S100A12 associates with CRP (ρ = 0.47; $p < 0.001$), IL-6 (ρ = 0.38; $p < 0.001$), and mAOPP (ρ = 0.26; p= 0.02), and negatively

with albumin (ρ = -0.27; $p < 0.05$), Kt/V (ρ= -0.22; $p = 0.06$), and GFR (ρ = -0.22; $p = 0.07$). Soluble RAGE levels associated negatively with BMI (ρ=-0.37; $p < 0.001$), FBMI (ρ= -0.34; $p < 0.05$), and LBMI (ρ=-0.37; $p < 0.05$).

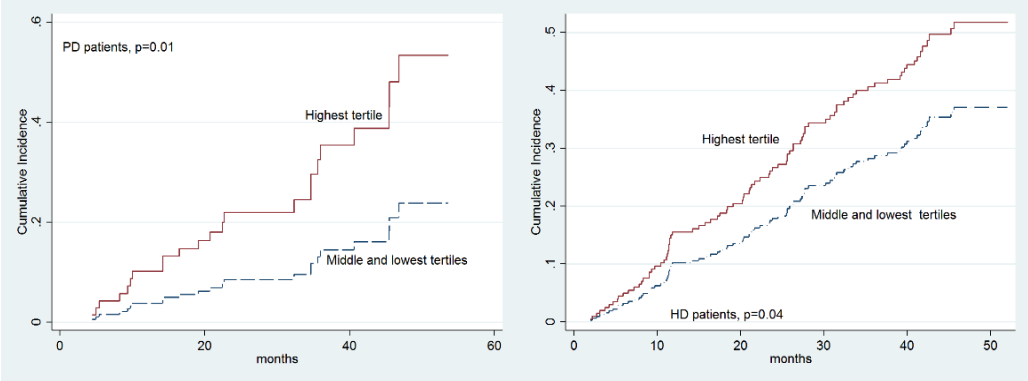
Multivariate logistic regression analysis showed that peripheral or cerebrovascular disease (PCVD) was associated mainly with high level of S100A12, OR=3.52 (CI, 1.09 – 11.41).

The mean follow-up for PD patients was 31 months, and during that time 23 PD patients died and 19 patients underwent kidney transplantation. Median S100A12 at baseline was higher in 23 non-survivors (36 [11 – 62] ng/mL, $p < 0.05$) than in 59 survivors who remained on PD (n = 40; 23 [16 – 31] ng/mL) or underwent renal transplantation (n = 19; 29 [23 – 54] ng/mL) while no such differences were found for sRAGE (p=0.26). The competing risk Cox regression analysis showed that the highest tertile of S100A12 versus the 2 other tertiles associated with increased mortality (**Figure 4.3 A**) No associations were found for sRAGE or S100A12/sRAGE ratio. In addition to high S100A12, presence of CVD was also a significant predictor of mortality in PD patients.

The median follow-up for HD patients was 29 months, and during that time 87 patients died and 38 underwent kidney transplantation. Median S100A12 at baseline was higher in non-survivors (n=87; 36 [11 – 62] ng/mL, $p < 0.01$) than in 103 survivors who remained on HD (n = 65; 23 [16 – 31] ng/mL) or who underwent renal transplantation (n = 38; 29 [23 – 54] ng/mL) while no such differences were found for sRAGE in HD patients (p=0.61). Similar to the case for PD patients, the competing risk Cox regression analysis showed that the highest tertile versus middle and lowest tertiles of S100A12 associated with increased mortality while no such associations were found for sRAGE or S100A12/sRAGE ratio (**Figure 4.3 B**). In addition to high S100A12, high age (>65 years) was also a significant predictor of mortality in HD patients.

Figure 4.3 Cumulative incidence rate for the competing end-point of renal transplantation and death in patients with highest tertile of S100A12 versus the lower tertiles of S100A12 in PD (Fig 4.3 **A**) and HD (Fig 4.3 **B**).

A **B**



In **study IV** we presented that S100A12, known to have a pro-inflammatory role, is associated with biomarkers of inflammation and with PCVD, suggesting that the mortality-predictive role of S100A12 is linked to vascular disease involving inflammatory mediators. We also presented that sRAGE, which is thought to be anti-inflammatory and protective against atherosclerotic CVD was not associated with inflammation, comorbidity and mortality. Interestingly, in prevalent PD patients, we found that sRAGE was inversely correlated to indices of body mass such as: BMI, FBMI, and LBMI. Levels of sRAGE are generally lower in patients with chronic inflammatory conditions, and plasma endogenous RAGE was reported to be inversely correlated with components of the metabolic syndrome including obesity (60). Also of interest in **study IV** was that S100A12, sRAGE, and S100A12/sRAGE levels were markedly elevated in PD patients. In the state of uraemia, the production of AGEs is increased resulting in up-regulation of RAGE which could promote peritoneal fibrosis and vascular sclerosis (97), and exposure to high glucose PD fluids may further contribute to such changes (98). Not surprisingly, sRAGE and S100A12 accumulate in PD patients (64, 65, 99) as shown also in the current study, and

hyperglycemia-induced reactive oxygen species may further increase expression of RAGE and RAGE-ligands (100).

Although the median S100A12 concentration was 1.9 times higher and the median S100A12/sRAGE ratio 2.4 times higher in PD patients than in HD patients, this difference could not be explained by the inflammation status as median CRP and IL-6 levels were higher in HD than in PD patients. We suggest that the difference may be related to differences between the two dialysis modalities implicating that stimulation of the AGE-RAGE system by glucose-based PD dialysis solutions could be of importance although it is likely that differences in patient characteristics or medications or other factors may also play a role.

Finally, in **study IV** we showed that high level of S100A12, in prevalent PD patients is associated with mortality. Our results are in accordance with previous studies showing similar results in patients with CKD stage 5 before starting dialysis (65) and in prevalent HD patients (66).

4.5 STUDY V

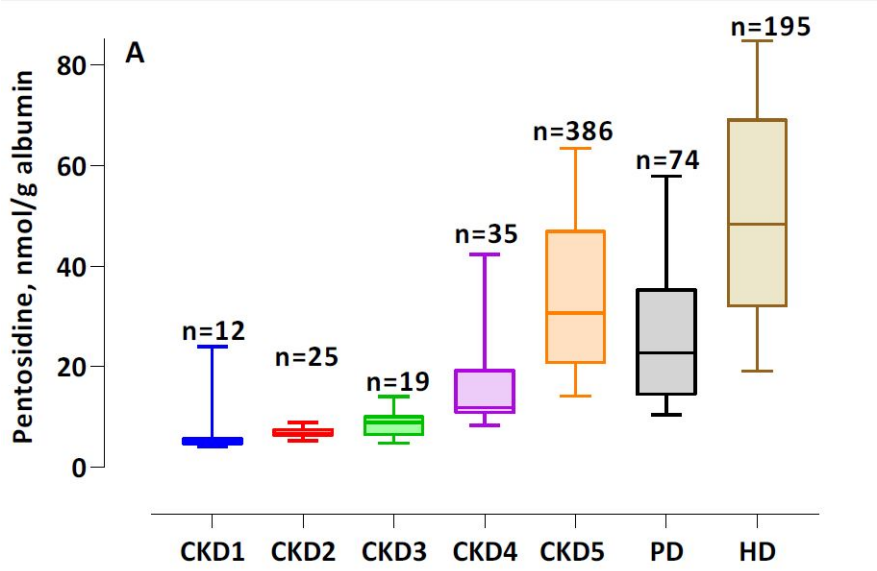
In **study V** we measured plasma pentosidine in 746 patients with different stages of CKD and undergoing different dialysis treatments including PD and HD, explored factors potentially linked to an increased level of pentosidine, and analysed the association of pentosidine with cardiovascular and all-cause mortality. The studied population consisted of 746 individuals with different stages of CKD including: CKD stage 1–2 (n=37) and CKD stage 3–4 (n=54), incident pre-dialysis CKD stage 5 patients (CKD5-ND; n=386) and prevalent PD (n=74) and HD (n=195) patients. The groups differed in regards to age with the youngest patients in the CKD5-ND group (median, 55 years) and the oldest in the CKD1-2 group (median, 68 years). Diabetes was most common in CKD stage 3–4 group (44%), and malnutrition (45%) and CVD (61%) most common among the HD patients. The highest level of inflammatory and oxidative stress biomarkers was also among HD patients (hsCRP: median 6.5mg/L and 8-OHdG: median 1.3 ng/ml).

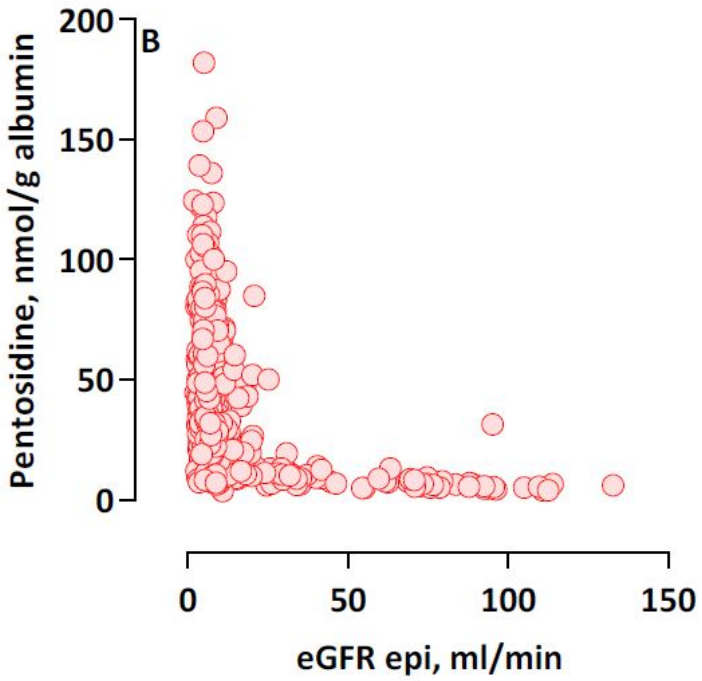
We observed a trend of increasing pentosidine level with the progression of CKD stages. Compared to CKD stage 1 group, CKD5-ND, and PD and HD patients had higher pentosidine

levels. The level of pentosidine in PD patients was significantly lower compared to HD patients, but not different compared to CKD5-ND patients (**Figure 4.4 A**)

Subgroup analysis showed no significant difference in plasma pentosidine levels between diabetes (DM) and non-diabetes (non-DM) patients in any of the group or for the combined cohort. In the combined cohort of all investigated individual (n=746) there were significant (all $p<0.0001$) correlations between plasma pentosidine and markers of inflammation (hsCRP, IL-6), oxidative stress (8-OHdG) and eGFR. **Figure 4.4 B** presents the relation between pentosidine and eGFR in all 746 individuals.

Figure 4.4 Baseline plasma pentosidine concentration, corrected for albumin level, and shown as box-and-whisker plots depicting median, and 10th to 90th percentile for each studied cohort (panel **A**). Correlations including all individuals (panel **B**; n=746) between plasma pentosidine level, corrected for albumin, and estimated glomerular filtration rate (eGFR) calculated by the chronic kidney disease epidemiology collaboration (CKD-EPI) formula or, in haemodialysis patients, assuming eGFR to be zero.





In the multivariate linear regression analysis, higher age, malnutrition (SGA), oxidative stress (8-OHdG, 1-SD higher), and belonging to the CKD5-ND, HD and PD cohorts were significant predictors of 1-SD higher pentosidine in the combined cohort of all 746 individuals after adjusting for sex, presence of DM, and inflammation (hsCRP). The applied model shows that being an ESRD patient (CKD5-ND, HD and PD cohorts) vs being a CKD 1–2 patient explains much of the variation in pentosidine level in parallel with higher age, malnutrition and oxidative stress.

The all-cause and cardiovascular mortality occurring within 60 months, in the combined group of all individuals (n = 746) was significantly associated with 1-SD higher pentosidine, RR = 1.04 (CI, 1.01–1.08, p = 0.01) and RR = 1.03 (CI, 1.01–1.06, p = 0.03) respectively, after adjustment for confounders: age, gender, CVD, DM, SGA, hsCRP (1-SD higher), 8-OHdG (1-SD higher) and cohort.

In **study V** we reported that plasma pentosidine is markedly elevated in patients with CKD and differed between the dialysis modalities (PD patients had significantly lower level of pentosidine compared to HD patients) suggesting that dialysis modality has an impact on

pentosidine level. High pentosidine concentration was associated with low GFR, and signs of oxidative stress and inflammation and, in addition, age, malnutrition, oxidative stress (8-OHdG) and group entities were significant predictors of a 1-SD higher pentosidine level. Thus, whereas variations in plasma pentosidine concentrations may to a large extent be explained by RRF, also higher age, an increased pro-oxidative state, and malnutrition, which are typical findings in uremic patients, as well as characteristics specific for each CKD stage or dialysis modality may also play a role. It was presented before that the accumulation of AGEs increases with the decline of renal function (69, 101). Studies in PD patients showed that loss of RRF is associated with increased plasma pentosidine and AOPP, showing the beneficial role of RRF in reducing oxidative and carbonyl stress (71). We found no significant differences in plasma pentosidine level between DM and non-DM patients in any of our studied cohort, and in multivariate analysis, DM was not a significant predictor of the pentosidine level. This may suggest that enhanced production and accumulation of AGEs among patients with impaired renal function is mainly related to conditions other than hyperglycaemia (102) and any added effect of glycation is attenuated by the effect of kidney failure and uremia (69). The survival analysis showed that 1-SD higher pentosidine was a significant, independent predictor of all-cause and CVD mortality after adjustment for confounders showing the putative usefulness of pentosidine as a biomarker and possible role as potential target for interventions aiming at improving clinical outcomes of patients with ESRD.

4.6 STRENGTHS AND LIMITATIONS

4.6.1 Strengths

As OPTiONS was a multicentre study in 6 European countries and 26 dialysis units our findings may be applicable in different settings thus increasing the external validity of the study. The broad inclusion criteria allowed the inclusion of all UPS patients and not only a selected group who professionals deemed to be appropriate for education. It is noteworthy that the study was conducted in real world clinical settings allowing monitoring of all aspects related to specific conditions of unplanned dialysis start. We also presented novel findings in regards to the area of patient education. In study I, we showed the feasibility and effectiveness of UPS-EP. In study II, we determined factors that may influence the educational pathway of the UPS patient and, in study III, we presented patient outcomes and healthcare utilisation in UPS patients depending on initial dialysis access (CVC or PD catheter) and subsequent patient pathway. In studies IV and V, we used the material from well phenotyped cohorts and presented novel findings regarding the prognostic role of biomarkers that are part of the AGE-RAGE pathway. In study IV, to the best of our knowledge, we are the first to show that a high level of S100A12 associates with mortality in prevalent PD patients. In study V, we presented determinants of plasma pentosidine in patients with various CKD stages and using different dialysis modalities and proved its association with cardiovascular and all-cause mortality.

4.6.2 Limitations

Several limitations in our studies should be acknowledged. In the OPTiONS study, patients were followed up for only 12 months; therefore we could only speculate about the long term clinical outcomes of patients who participated in the study. The study had non-interventional design with no control group; however the ethical aspect of including a control group should be noted as inclusion of controls would result in deprivation of the education in one of the included groups. We had no biochemical measurements available and we did not monitor the levels of biomarkers in the OPTiONS study; such information could have provided clinically relevant information and increased the value of the study. Also we did not follow patients prior to enrolment; thus we were unable to analyse the pre-dialysis factors related to the dialysis initiation. In the biomarker studies, due to cross sectional nature of study IV and V, we are unable to state any conclusion about causality of the observed association of mortality with

S100A12, sRAGE and pentosidine. We collected samples for measurement of biomarkers only at a single time point (baseline); therefore, we could not speculate about the variations of the investigated biomarkers over time.

5. ACKNOWLEDGEMENTS

During my PhD journey my paths have crossed with many people, without whom I would not be able to complete my thesis. I would like to thank everyone and especially acknowledge the ones mentioned below.

Bengt Lindholm, my main supervisor for giving me the unique opportunity to be a PhD student at the Division of Baxter Novum and Renal Medicine at Karolinska Institutet. Thank you for sharing your endless knowledge in the nephrology field, research experience and positive attitude. I am grateful for your encouragement, precious advices and guidelines for my research and personal life at many decisive moments during the last four years. You are a great example I would like to follow during my future career development.

I am utmost grateful to my supervisor **Peter Rutherford** for believing in me from the beginning and involving me in the European Training and Research in Peritoneal Dialysis (EuTRiPD) programme. Thank you for introducing me to the international scientific community, and making my PhD project challenging and rewarding. I appreciate your support, patience and that you were always available for me. It was a privilege to learn from you and be supervised by you.

Abdul Rashid Qureshi, my supervisor and the statistical guard of my PhD project for many hours of statistics lessons. Thank you for your help during the projects and standing by my side during the crucial moments of my PhD. The guidance in statistical field I received from will be fundamental in my future career.

Juan Jesus Carrero and **Olof Heimburger,** my co-supervisors, thank you for sharing your vast expertise in the nephrology and epidemiology field, your guidance and support during my PhD project.

Peter Stenvinkel and **Peter Barany,** co-authors, thank you for your always constructive and valuable comments which contributed to and increased the value of my work.

Paul Leurs, co-author and friend, thank you for precious advices along the way, and never-ending scientific and motivational talks.

The work presented in this thesis would not be possible without all the work done in the department by **Bjorn Anderstam**, head of Renal Laboratory, **Monika Ericsson** and **Ann-Christin Bragfors-Helin,** lab technicians at the Clinical Research Centre (KFC). Thank you for handling the samples and making biomarkers research possible**.**

I would like to express my gratitude to all members of EuTRiPD consortium: principal investigators (**Rob Beelen**, **Christoph Aufricht**, **Klaus Kratochwil**, **Donald Fraser**, **Matthias Eberl**, **Nicholas Topley**, **Manuel Lopez–Cabrera**, **Claus Peter Schmitt**, **Michel Fischbach**, **Janusz Witowski Achim Jorres** and **Peter Rutherford**) and students (**Silvia Tarantino**, **Edyta Kawka**, **Anna Rita Liuzzi**, **Melisa Lopez Anton**, **Evelina Ferrantelli**, **Maria Bartosova**, **Katarzyna Bialas**, **Ilse Calm**, **Georgios Liappas**, **Mark Via** and **Andras Rudolf**) for creating the most friendly and stimulating scientific environment, that any researcher may wish for. Thank you for transferring your knowledge and expertise during our meetings across Europe. I am very grateful that I could collaborate with you all. The excellent project coordination would not be possible without our project manager **Tanja van Wier** who showed us all how to meet the deadlines.

Special thanks to all researchers who have been working at and visited Baxter Novum during my stay: **Elvia Garcia-Lopez**, **Hong Xu**, **Jia Sun**, **Ting Jia**, **Xioyan Huang**, **Thiane Gama-Axelsson**, **Desiree Luis Rodrigues**, **Jacek Waniewski, Magdalena Jankowska, Beatriz Fernandez-Fernandez**, **Gloria Lisette Sencion**, **Maria Molina**, **Naohito Isoyama**, **Hideyuki Mukai**, **Pei Ming, Dai Lu, Martin Schalling, Louise Nordfors, Jose Divino, Maria Chan**, **Shirley Yumi Hayashi**, **Marcelo Nascimento**, **Sun-Hee Park**, **Michal Chmielewski** and many others**-** you all make this place unique!

My co-workers in Baxter Healthcare R&D in Belgium: **Magdalena Wlodarczyk**, **Milena Opacic**, **Vanja Pinoie**, **Marie-Florence Ngole-Nse**, **Goedele Paternot**, **Cathy Coulon**, **Isabelle Tytgat**, **Delphine Callemien**, **Bart Dios,** thank you for sharing your experience and all nice moments during lunch and coffee breaks.

My frequent mobility and managing of two administrational worlds in Sweden and Belgium would not be possible without support of **Evianne Larsson** and **Valerie Libeau**. You made it all easy and accessible. Thank you!

I am very lucky that my paths have crossed with amazing people who became my friends. I would like to express my utmost gratitude to **Gabriela Cobo** for being all in one: true friend, great flatmate and co-worker. Thank you for always being there for me; sharing together all beautiful, funny and sometimes tough moments made my life in Stockholm unforgettable. I truly believe that the distance will never matter for us!

Juliana Cordeiro, Rute Aguiar, **Alessandro Gasparini**, **Nikos Kyriakidis** thank you for being my Swedish family, great friends and the best flatmates I could ever wish for.

I cannot forget about my dear friends from Poland: **Kasia**, **Robert**, **Piotrek**, **Marcin** and many others who regardless the distance were the truest supporters of my actions.

The completion of this thesis would not be possible without support of my family: **Slawek**, my brother **Michal**, grandparents **Michal** and **Irena.** Thank you for believing in me and making me feel that home is not so distant. (*Napisanie tej pracy nie byloby mozliwe bez wsparcia mojej rodziny: Slawek, brat Michal, dziadkowie Michal i Irena. Dziekuje Wam za to, ze zawsze wierzycie we mnie i sprawiacie, ze nigdy nie czuje, ze jestem daleko od domu).*

I would like to express my endless love and gratefulness to **my mother Barbara** for educating me, raising me with noble values and showing me that I can reach everything I dream about. Thank you for your unconditional love and invaluable support at any moment of my life. (*Pragne wyrazic moja ogromna milosc i wdziecznosc dla mojej mamy Barbary za wysztalcenie, wychowanie, wpojenie szlachetnych wartosci i pokazanie mi, ze moge osiagnac wszystko o czym tylko zamarze*. *Dziekuje za bezwarunkowa milosc i nieocenione wsparcie w kazdym momencie mojego zycia)*.

And last but not least, I am the most grateful to my boyfriend **Lauro** for love, stoic patience and remarkable support every day and during the most difficult and stressful moments. Thank you for cheering me up and always making me laugh. It is absolutely amazing to having you by my side!

This PhD project was part of European Training and Research in Peritoneal Dialysis (EuTRiPD) programme (www.eutripd.eu) and supported by the European Union **Marie Curie Initial Training Network** grant (Call: FP7-PEOPLE-2011-ITN) .

I would like to recognise the support of **Baxter Healthcare** for the final year of my PhD project.

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