RESEARCH, DESIGN AND DEVELOPMENT OF SW TOOLS
FOR PROCESS MANAGEMENT IN THE AREA OF E–HEALTH

Projection of future number of End-Stage Renal Disease patients in Greece

PH.D. THESIS

ANASTASSIA RODINA-THEOCHARAKI

PATRAS 2012
ΕΡΕΥΝΑ, ΣΧΕΔΙΑΣΜΟΣ ΚΑΙ ΑΝΑΠΤΥΞΗ ΕΡΓΑΛΕΙΩΝ ΛΟΓΙΣΜΙΚΟΥ ΓΙΑ ΤΗ ΔΙΑΧΕΙΡΙΣΗ ΔΙΑΔΙΚΑΣΙΩΝ ΣΤΟΝ ΤΟΜΕΑ ΤΗΣ ΗΛΕΚΤΡΟΝΙΚΗΣ ΥΓΕΙΑΣ

Πρόβλεψη μελλοντικού αριθμού ασθενών με Τελικού Σταδίου Χρόνια Νεφρική Ανεπάρκεια στην Ελλάδα

ΔΙΔΑΚΤΟΡΙΚΗ ΔΙΑΤΡΙΒΗ

ANASTASSIA RODINA-THEOCHARAKI
Three-Member Advisory Committee

Nicolas Pallikarakis
(Supervisor)                  Professor, School of Medicine, University of Patras

Dimitrios Koutsouris
Professor, School of Electrical and Computer Engineering, National Technical University of Athens

Eleni Kaldoudi
Associate Professor, School of Medicine, Democritus University of Thrace

Seven Members Examination Committee

Nicolas Pallikarakis
(Supervisor)                  Professor, School of Medicine, University of Patras

Dimitris Koutsouris
Professor, School of Electrical and Computer Engineering, National Technical University of Athens

Eleni Kaldoudi
Associate Professor, School of Medicine, Democritus University of Thrace

Dimitris Goumenos
Professor, School of Medicine, University of Patras

Chryssoula Labropoulou-Karatza
Professor, School of Medicine, University of Patras

Adamantia Mitsacou
Professor, School of Medicine, University of Patras

Konstantinos Gyftopoulos
Associate Professor, School of Medicine, University of Patras
Τριμελής Συμβουλευτική Επιτροπή

Νικόλαος Παλληκαράκης (Επιβλέπων) Καθηγητής Τμήματος Ιατρικής, Πανεπιστήμιο Πατρών

Δημήτριος Κοντσούρης Καθηγητής Σχολής Ηλεκτρολόγων Μηχανικών και Υπολογιστών, Εθνικό Μετσόβιο Πολυτεχνείο

Ελένη Καλδούδη Αναπληρωτρια Καθηγήτρια Τμήματος Ιατρικής, Δημοκρίτειο Πανεπιστήμιο Θράκης

Επταμελή Εξεταστική Επιτροπή

Νικόλαος Παλληκαράκης (Επιβλέπων) Καθηγητής Τμήματος Ιατρικής, Πανεπιστήμιο Πατρών

Δημήτριος Κοντσούρης Καθηγητής Σχολής Ηλεκτρολόγων Μηχανικών και Υπολογιστών, Εθνικό Μετσόβιο Πολυτεχνείο

Ελένη Καλδούδη Αναπληρωτρια Καθηγήτρια Τμήματος Ιατρικής, Δημοκρίτειο Πανεπιστήμιο Θράκης

Δημήτριος Γούμενος Καθηγητής Τμήματος Ιατρικής, Πανεπιστήμιο Πατρών

Χρυσούλα Λαμπροπούλου-Καραντζά Καθηγήτρια Τμήματος Ιατρικής, Πανεπιστήμιο Πατρών

Αδαμάντια Μητσάκου Καθηγήτρια Τμήματος Ιατρικής, Πανεπιστήμιο Πατρών

Κωνσταντίνος Γκοτόπουλος Αναπληρωτής Καθηγητής Τμήματος Ιατρικής, Πανεπιστήμιο Πατρών
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SUMMARY

End Stage Renal Disease (ESRD) is the irreversible loss of kidney function, which can be due to various causes. Its treatment is one of the most costly chronic disease treatments. There are now approximately one million people worldwide living with ESRD and this number is predicted to increase in the future. The main reasons for the increasing incidence of ESRD worldwide are population ageing, the rapid increase of diabetes mellitus reaching epidemic proportions, and changes in age limits for treatment initiation.

In Greece, during the period 2005-2009, 74% of the ESRD patients were on hemodialysis (HD), 7% on peritoneal dialysis (PD) and 19% were living with a functioning graft. The latter percentage brings Greece in the 26th place out of 36 countries in prevalence of functioning grafts worldwide. Cost-effectiveness analyses of these treatments have shown that RTx is overall the least expensive, followed by PD, while centre HD is the most expensive. Moreover, these treatments are also listed in the exact same order concerning the quality of life they provide to patients. The main reasons for the low RTx rate in Greece are the lack of organ donation, largely due to inadequate information, the inefficient organ distribution system, a high number of private HD centers not interested in RTx, as well as social factors.

The objective of the present work was to implement a model for the projection of the ESRD patients’ number by 2020 in Greece and investigate the impact of different scenarios of an increase in RTx. In addition, a cost-effectiveness analysis of the increase in RTx was performed. The projection was performed based on a Markov chain model. The Markov models are distinguished by their simplicity and their ability to accurately represent many clinical problems.

A deterministic Markov chain model was implemented in order to predict the future number of prevalent ESRD patients in Greece. Monte Carlo techniques were applied in order to add robustness to the model. Thus two models of prediction were implemented, a Markov chain and a Markov Chain Monte Carlo (MCMC) model. Age-specific data (<45, 45-65, >65 age groups) on incident and prevalent ESRD patients’ number for Greece, available from the European Renal Association – European Dialysis and Transplant Association reports for the period 1998-2009, were used for the implementation. The basic component of the Markov chain is the transition matrix defining the probability for the patient to move between the four states, i.e. HD, PD, RTx and death. An iterative error minimization technique was used in defining the transition probabilities of the Markov chain, based on the data from 1998 to 2006. Both Markov chain and MCMC models were successfully validated based on data for the period from 2007 to 2009. In each model the ESRD incident patients’ number in Greece
was predicted in a different way. For the Markov chain model three incidence rate scenarios were applied: low, medium and high. Additionally, two different approaches were proposed for the increase in RTx, one for each model. In the Markov chain model, two scenarios of RTx increase were applied on the number of prevalent patients. The first one was based on the assumption that the average number of transplants performed in Greece during the period 2005-2009 will double by 2020. The second one assumed that Greece will reach by 2020 the transplantation rate of Norway in 2009, the highest transplantation rate reported during that year worldwide. In the MCMC model, the increase of RTx was accomplished by increasing annually by 1% the number of incident patients receiving RTx and reducing accordingly the number of patients performing HD.

The Markov chain model projected an increase in the number of prevalent patients’ in Greece by 19.3%, 24.4% and 42.2% in 2020 compared to 2009, depending on the incidence scenario applied. Similarly, the MCMC model projected a 25.0% prevalence increase. In the Markov chain model, the results of the increase in RTx indicated that in 2020 there will be a 64.6% (first scenario) or a 107.2% (second scenario) increase in the number of RTx patients compared to 2009, resulting in total saving of €50.2 and €112.37 million, respectively, for the period 2010-2020. Finally, the increase in RTx accomplished in the MCMC model indicated a 57.9% increase of patients living with a transplanted kidney, resulting in total saving of €68.2 million.

The results of both models suggest that performing more kidney transplantations instead of HD would reduce the treatment costs for the country’s healthcare system, while at the same time it would improve the quality of life for a significant number of ESRD patients.
Η Τελικού Σταδίου Χρόνια Νεφρική Ανεπάρκεια (ΤΣΧΝΑ) είναι η μη αναστρέψιμη απώλεια της νεφρικής λειτουργίας, η οποία μπορεί να οφείλεται σε διάφορα αίτια. Η θεραπεία της είναι μία από τις πιο δαπανηρές όσον αφορά τις χρόνιες παθήσεις. Σήμερα, υπολογίζεται ότι περίπου ένα εκατομμύριο άνθρωποι παγκοσμίως ζουν με ΤΣΧΝΑ, ενώ ο αριθμός τους προβλέπεται να αυξηθεί στο μέλλον. Οι κύριοι παράγοντες αύξησης της επίπτωσης (δηλαδή του αριθμού των νεοεντασσόμενων ασθενών) της ΤΣΧΝΑ παγκοσμίως είναι η αύξηση της μέσης ηλικίας του πληθυσμού, η αλματώδης αύξηση του σακχαρώδους διαβήτη που λαμβάνει επιδημικές διαστάσεις, καθώς και οι αλλαγές στα ηλικιακά όρια για έναρξη θεραπείας.

Στην Ελλάδα, κατά την περίοδο 2005-2009 το 74% ασθενών με ΤΣΧΝΑ έκανε αιμοκάθαρση, το 7% έκανε περιτοναϊκή κάθαρση και το 19% ζούσε με νεφρικό μόσχευμα. Ο τελευταίο ποσοστό κατατάσσει την Ελλάδα στην 26η θέση ανάμεσα σε 36 χώρες παγκοσμίως όσον αφορά τον αριθμό των ασθενών που ζούν με μεταμοσχεύμενο νεφρό. Η ανάλυση κόστους-αποτελεσματικότητας δείχνει ότι η λιγότερο δαπανηρή θεραπεία της ΤΣΧΝΑ είναι η μεταμόσχευση, ακολουθούμενη από την περιτοναϊκή κάθαρση, ενώ η αιμοκάθαρση αναδεικνύεται ως η πιο δαπανηρή. Οι θεραπείες κατατάσσονται με την ίδια ακριβώς σειρά όσον αφορά και την ποιότητα ζωής που παρέχουν στους ασθενείς. Οι βασικές αιτίες για το χαμηλό ποσοστό μεταμοσχεύσεων στην Ελλάδα είναι η έλλειψη δωριζόμενων οργάνων, που οφείλεται κατά πολύ στην ελλιπή πληροφόρηση, η ανεπάρκεια του συστήματος διανομής οργάνων, ο υψηλός αριθμός ιδιωτικών κέντρων αιμοκάθαρσης, τα οποία δεν ενδιαφέρονται για μεταμοσχεύσεις, καθώς και κοινωνικοί παράγοντες.

Ο σκοπός της παρούσας διατριβής ήταν η υλοποίηση ενός μοντέλου για την πρόβλεψη του αριθμού των ασθενών με ΤΣΧΝΑ στην Ελλάδα το 2020, καθώς επίσης και η διερεύνηση της επίδρασης διαφόρων σεναρίων αύξησης των μεταμοσχεύσεων. Επιπλέον, πραγματοποιήθηκε ανάλυση κόστους-αποτελεσματικότητας της Αιμοκάθαρσης για την αξιολόγηση της απόδοσης της ανάπτυξης του μοντέλου. Ο σχεδιασμός μιας αλυσίδας Μαρκόφ βασίζεται στον πίνακα μετάβασης για υπολογισμό της πιθανότητας μετακίνησης του ασθενούς ανάμεσα στη Αιμοκάθαρση.
την περιτοναϊκή κάθαρση, τη μεταμόσχευση και τον θάνατο. Για να υπολογιστούν οι πιθανότητες μετάβασης στην αλυσίδα Μαρκόφ, έγινε χρήση μιας επαναληπτικής τεχνικής μείωσης του σφάλματος με βάση τα ηλικιακά δεδομένα της περιόδου 1998-2006. Και τα δύο μοντέλα επαληθεύτηκαν επιτυχώς με βάση τα δεδομένα της περιόδου 2007-2009. Η πρόβλεψη του μελλοντικού αριθμού νεοεντασσόμενων ασθενών με ΤΣΧΝΑ στην Ελλάδα έγινε με διαφορετικό τρόπο σε κάθε μοντέλο. Στο μοντέλο Μαρκόφ, εφαρμόστηκαν τρία διαφορετικά σενάρια πρόβλεψης του ποσοστού επίπτωσης: χαμηλό, μεσαίο και υψηλό. Επιπλέον, σε κάθε μοντέλο ακολουθήθηκε διαφορετική προσέγγιση όσον αφορά την αύξηση του αριθμού των μεταμοσχεύσεων. Στο μοντέλο Μαρκόφ, εφαρμόστηκαν δύο σενάρια αύξησης των μεταμοσχεύσεων σε σχέση με τον αριθμό των ασθενών σε ΘΥΝΔΑ. Το πρώτο σενάριο βασίστηκε στην υπόθεση ότι ο μέσος αριθμός μεταμοσχεύσεων που έγιναν στην Ελλάδα κατά την περίοδο 2005-2009 θα διπλασιαστεί ως το 2020. Στο δεύτερο σενάριο θεωρήθηκε ότι η Ελλάδα θα φτάσει ως το 2020 το ποσοστό μεταμοσχεύσεων της Νορβηγίας το 2009, που ήταν το μεγαλύτερο παγκοσμίως για το έτος. Στο μοντέλο Μαρκόφ Μόντε Κάρλο, η αύξηση του αριθμού των μεταμοσχεύσεων επιτεύχθηκε με την κατά 1% του αριθμού των νεοεντασσόμενων ασθενών που θα έκαναν μεταμόσχευση, με αντίστοιχη μείωση του αριθμού των αιμοκαθαιρόμενων.

Το μοντέλο Μαρκόφ προέβλεψε αύξηση του αριθμού των ασθενών στην Ελλάδα κατά 19.3%, 24.4% και 42.2% το 2020 σε σχέση με το 2009, ανάλογα με το εφαρμοζόμενο σενάριο επίπτωσης. Το μοντέλο Μαρκόφ Μόντε Κάρλο προέβλεψε αντίστοιχη αύξηση της τάξης του 25%. Στο μοντέλο Μαρκόφ, τα αποτελέσματα της αύξησης των μεταμοσχεύσεων έδειξαν ότι το 2020 θα υπάρξει αύξηση κατά 64.4% (πρώτο σενάριο) ή κατά 107.2% (δεύτερο σενάριο) του αριθμού των μεταμοσχευμένων ασθενών συγκριτικά με το 2009, με συνολική εξοικονόμηση 50.2 και 112.37 εκατομμύρια ευρώ αντίστοιχα, για την περίοδο 2010-2020. Τέλος, η αύξηση του αριθμού των μεταμοσχεύσεων στο μοντέλο Μαρκόφ Μόντε Κάρλο έδειξε αύξηση κατά 57.9% του αριθμού των ασθενών που ζουν με μεταμοσχευμένο νεφρό, με συνολική εξοικονόμηση 68.2 εκατομμύρια ευρώ.

Τα αποτελέσματα και στα δύο μοντέλα καταδεικνύουν ότι η αύξηση του αριθμού των μεταμοσχευμένων έναντι της αιμοκάθαρσης θα μείωσε το κόστος θεραπείας για το Σύστημα Υγείας της χώρας, ενώ ταυτοχρόνως θα βελτίωσε την ποιότητα ζωής για έναν σημαντικό αριθμό ασθενών με ΤΣΧΝΑ.
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<td>LY</td>
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<td>MCMC</td>
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<td>PD</td>
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<td>pmp</td>
<td><strong>per million population</strong></td>
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<td>QALY</td>
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To my parents and husband
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Chapter 1
INTRODUCTION

1.1 MOTIVATION

There are now approximately one million people worldwide living with End-Stage Renal Disease (ESRD) with prediction of continuous patients’ number increase in the future. Population aging, prevalence in type 2 diabetes mellitus and hypertension are factors implicated in the development of Chronic Kidney Disease (CKD) and considered the most important causes of increased prevalence of ESRD (Passa 2002; White, Chadban et al. 2008). It has been reported that during the period 1997-2006, the overall adjusted prevalence in Europe had a 2.7% annual linear increase and is predicted to continue to influence the demand for Renal Replacement Therapy (RRT) and Renal Transplantation (RTx) (Kramer, Stel et al. 2009).

According to the annual report published in 2011 by the United States Renal Data System (USRDS) concerning the year 2009, Greece is in the 8th place in incidence out of 42 countries worldwide and 2nd after Luxembourg in Europe. At the same time, the country is reported to be in the 13th place worldwide in prevalence and
3rd after Belgium and France in Europe \textit{(USRDS 2011)}. RRT and RTx are costly lifelong treatments for ESRD patients, severely affecting their quality of life (QOL). Increase in ESRD prevalence and treatment demand has led to crucial financial issues for the healthcare authorities.

During the period 2005-2009, on average 74\% of the ESRD patients in Greece were on Hemodialysis (HD), 7\% on Peritoneal Dialysis (PD) and 19\% were living with a functioning graft. The latter percentage brings Greece in the 26th place out of 36 countries in prevalence of functioning graft worldwide \textit{(USRDS 2011)}. The choice of treatment modality for the ESRD patients is influenced by different factors, such as financial expenditure, services’ organization, resource availability, access and quality of healthcare, adoption of medical technology and patients’ medical conditions. Several investigations have come to the conclusion that RTx, Home Hemodialysis (HHD) and PD are more cost-effective than Centre Hemodialysis (CHD) \textit{(Winkelmayer, Weinstein et al. 2002; Just, Riella et al. 2008)}. A study by Kramer \textit{et al.} (2009) covering the period 1997-2006 reported that survival rates on PD and RTx improved \textit{(Kramer, Stel et al. 2009)}. At the same time transplanted patients’ QOL was evaluated as comparable to that of the general population \textit{(Evans, Manninen et al. 1985; Kramer, Stel et al. 2009)}. Therefore, it is suggested that increasing the number of RTx and introducing HHD (which is presently not available in Greece) may significantly improve patients’ QOL and decrease financial expenses.

The rough estimation of the future number of ESRD patients represents a very crucial issue for any health system. Projecting the number of patients with ESRD is considered to be a valuable tool for healthcare decision makers in order to achieve more efficient resource allocation and management. Stepwise autoregressive methods, exponential smoothing models and Markov models are mathematical approaches that are commonly used in projection studies. The most common approach, used to predict the number of patients with chronic diseases, is the Markov model. Markov models are distinguished by their simplicity and their ability to faithfully represent many clinical problems. Markov models were used to evaluate and describe the progress of diabetic retinopathy \textit{(Marshall and Jones 1995)}, human immunodeficiency virus \textit{(Hendriks, Satten et al. 1996)} as well as to evaluate the QOL of children with cancer \textit{(Bradlyn, Ritchey et al. 1996)}. Several authors have employed Markov models for economic evaluation and cost-effectiveness analysis of the treatment of patients with

Modelling of chronic diseases is useful when the impact of different factors (e.g. change in incidence, change in patients’ distribution by therapy, introduction of new treatments) may be studied in long term projection. Markov chain models are among the techniques that allow the easy evaluation of the impact of these factors on systems’ overall behaviour.

1.2 OBJECTIVES AND TECHNIQUES OF THE STUDY

The main objective of this work was to design, implement and evaluate a model for prediction of the future number of ESRD prevalent patients in Greece for the period 2010-2020. Additionally, the impact of different scenarios of increase in the number of transplantations was investigated and cost-effectiveness analysis was performed. For this purpose a Markov chain model was used to create a deterministic model for ESRD patients’ projection for Greece. In order to account for uncertainties from input model parameters, Monte Carlo techniques were introduced. Thus two prediction models were implemented: a Markov chain model and a Markov Chain Monte Carlo (MCMC) model.

The basic component of the Markov chain is the Transition Matrix (TM) that determines the transitions of patients between therapies. An iterative error minimization technique was used to estimate the TMs for Greece based on national and international data. For the purpose of this work the data on incident and prevalent patients were classified in three age groups: younger than 45 (<45), between 45 and 65 (45-65) and older than 65 (>65) years. Age-specific data on the number of incident
and prevalent patients with ESRD for Greece, available from the European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) reports for the period 1998-2009, were used for the implementation of the model.

The number of incident patients with ESRD was projected in two ways: in numbers by age group and in total per million population (pmp) taking into account the general population growth in Greece to the year 2020. Two different approaches were proposed for the increase in RTx rates in Greece, one for each model. The impact of increasing RTx and reducing accordingly the number of HD was implemented and economical estimates were performed. This is the first time that an attempt to project ESRD patients’ number to the nearest future is performed for Greece.

1.3 THESIS OUTLINE

A general introduction to kidney function and description of ESRD are presented in the second chapter of this thesis. ESRD is the complete or almost complete loss of kidney function requiring RRT: any form of chronic dialysis or RTx. There are two widely used basic measures of the amount of the disease in population: incidence and prevalence rate, whose definitions are provided in the 2nd chapter. The last part of the chapter is dedicated to the description of ESRD patients’ treatment modalities, among which HD or PD, and RTx are the main types.

The 3rd chapter is devoted to the review of the ESRD epidemiology. Review of ESRD patients’ QOL, RRT and RTx costs and general trends of the ESRD incidence and prevalence are presented. The chapter closes with the review of ESRD epidemiology and treatment modalities management in Greece, problems faced by the patients and healthcare authorities.

The 4th chapter is dedicated to the Markov models theory. The characteristics of the model are described in detail. Then, the Markov chain model implementation in medical decision problems is presented. Techniques for model validation are discussed further on in the chapter. Finally, the chapter describes the incorporation of Monte Carlo techniques into the Markov chain model.
The Markov chain model TMs estimator for the ESRD patients in Greece is described in the 5th chapter of this thesis. The data splitting of the available data is presented and the iterative minimization technique is explained. Finally, the training and the validation techniques are presented.

The 6th chapter describes the details of the implemented Markov chain model including incidence projection, higher RTx rate scenarios applied on prevalent patients and cost-effectiveness analysis used for the prediction of the future costs. The results of the estimated TMs are presented together with the model validation and model uncertainty analysis. The results of the future ESRD patients’ number projection from 2010 to 2020 are described and discussed.

The 7th chapter deals with the MCMC model for the ESRD patients’ projection in Greece. Detailed input parameters to the simulation model, like incidence projection and higher RTx rate scenario applied on incident patients, are described. The results of the model validation are summarized. The results of the simulated model that include projection of the future patients’ number to 2020 and the results of applying the scenario of increase in RTx and its impact on the cost-effectiveness of the ESRD patients’ treatment in Greece are presented and discussed.

Model limitations are reviewed and discussed in the last chapter. Conclusions and future work perspectives are outlined at the end of the chapter.
Chapter 2

KIDNEY FUNCTION AND END-STAGE RENAL DISEASE

2.1 KIDNEY FUNCTION

The kidneys are paired organs that lie high in the abdomen on its posterior wall either side of the vertebral column. In the adult human, each kidney is about 11 cm in length and 6 cm wide and weighs between 115 and 170 g. The kidneys are responsible for excretory and regulatory functions in human body. By excreting water and solutes, the kidneys rid the body of excess water and waste products. They also regulate the volume and composition of body fluids within a very narrow range, despite wide variations in the intake of food and water.

Kidneys represent about 0.5% of the total weight of the body, but receive 20–25% of the total arterial blood pumped by the heart. Human kidneys serve to convert more than 1700 liters of blood per day into about 1 liter of highly specialized concentrated fluid called urine.
In human body kidneys serve several functions, including:

1. Regulation of body fluid osmolality and volumes;
2. Regulation of electrolyte balance;
3. Regulation of acid-base balance;
4. Removal of metabolic waste products and foreign substances from the blood and their excretion in the urine;

Each of these functions is essential for human beings. The control of body fluid osmolality is important for the maintenance of normal cell volume in all tissues of the body. Control of the volume of the body fluids is necessary for normal function of the cardiovascular system. The kidneys, working in concert with components of the cardiovascular, endocrine, and central nervous systems, accomplish these tasks by regulating the excretion of water and NaCl.

The kidneys play an essential role in regulating the amount of several important inorganic ions in the body, including Na⁺, K⁺, Cl⁻, HCO₃⁻, H⁺, Ca²⁺, and PO₄³⁻. To maintain appropriate balance, the excretion of these electrolytes must be equal to their daily intake. For many electrolytes, the kidneys are the sole or primary route through which they are excreted.

Another important role of the kidneys is the regulation of acid-base balance. Many of the metabolic functions of the body are extremely sensitive to pH. Thus, the pH of the body fluids must be maintained within narrow limits. The pH is maintained by buffers within the body fluids and by the coordinated action of the lungs, liver and kidneys.

The kidneys also excrete a number of end products of metabolism that are no longer needed by the body. These waste products include urea, uric acid, creatinine, end products of hemoglobin metabolism, and metabolites of hormones. The kidneys also eliminate foreign substances from the body, such as drugs, pesticides, and other chemicals ingested in food.

Finally, the kidneys are important endocrine organs that produce and secrete renin, calcitriol, and erythropoietin. Renin activates the renin-angiotensin-aldosterone system, which helps regulate blood pressure and sodium and potassium balance.
Calcitriol, a metabolite of vitamin D₃, is necessary for normal reabsorption of Ca²⁺ by the gastrointestinal tract and for its deposition in bone. Erythropoietin stimulates red blood cell formation by the bone marrow. Decreased erythrocyte production is a cause of the anemia seen in CKD.

Each kidney is composed of approximately 1 million functional units, called nephrons, bound together by small amounts of connective tissue, which contains blood vessels, nerves, and lymphatics. Each nephron consists of an initial filtering component called the renal corpuscle, and a tubule that extends out from the renal corpuscle. The renal corpuscle produce a filtrate from blood that is free of cells and proteins. This filtrate then leaves the renal corpuscle and enters the tubule, where it is processed before exiting the kidney as urine. The diagram of basic kidney function is presented in Figure 2.1.

![Diagram of basic healthy kidney function. Source: Taken from CancerHelp UK, the patient information website of Cancer Research UK: http://cancerhelp.cancerresearchuk.org with the permission.](image)

In order to define the exact level of renal function, the Glomerular Filtration Rate (GFR) is measured. In health, the GFR remains remarkably constant owing to intrarenal regulatory mechanism. In disease, with a reduction in intrarenal blood flow, damage to or loss of glomeruli (the tiny units located within the kidneys that are responsible for the filtration of waste products from the blood), or obstruction to the
free flow of ultrafiltrate along the tubule, the GFR will fall and the ability to eliminate waste material and to regulate the volume and composition of body fluid will decline. It is essential that the serum (plasma) urea or creatinine is within the normal range. There are two formulas widely used to estimate GFR. The first and most frequently used is the Cockcroft-Gault formula (Kasper, Braunwald et al. 2004), which accounts for age and muscle mass:

$$\text{Creatinine clearance (mL/min) = } \frac{(140 - \text{age}) \times \text{lean body weight(kg)}}{\text{plasma creatinine(mg/dL)} \times 72}$$  \hspace{1cm} \text{Eq. 2-1}

The second formula is based on data derived from Modification of Diet in Renal Disease (Kasper, Braunwald et al. 2004):

$$\text{GFR(mL/min) per } 1.73m^2 = 186.3 \times P_Cr(e^{-1.154}) \times \text{age}(e^{-0.203}) \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$  \hspace{1cm} \text{Eq. 2-2}

where $P_Cr$ is plasma creatinine.

The Modification of Diet in Renal Disease equation unlike Cockroft-Gault also considers racial background of the patient, which makes it more reliable in ethnically diverse groups of individuals.

General information on kidney anatomy, physiology, pathology can be found in several textbooks (Vander, Sherman et al. 1994; Berne and Levy 1998; Kasper, Braunwald et al. 2004; Kumar and Clark 2005; Kumar, Abbas et al. 2005; Fauci, Braunwald et al. 2008).

2.2 END-STAGE RENAL DISEASE

Chronic kidney disease is a pathophysiologic process with multiple etiologies, resulting in the inexorable attrition of nephron number and function and frequently leading to ESRD. In turn, ESRD represents a clinical state or condition in which there has been an irreversible loss of renal function, in sufficient degree to render the patient permanently dependent upon RRT in order to avoid life-threatening uremia. Uremia is the clinical and laboratory syndrome, reflecting dysfunction of all organ systems as a result of untreated or undertreated acute or chronic renal failure. Given the capacity of the kidneys to regain function following acute injury, the vast majority (>90%) of patients with ESRD have reached this state as a result of CKD (Kasper,
Braunwald et al. 2004). A gradual worsening of kidney function of a person with CKD may last for 10 - 20 years or more before progressing to ESRD.

There is a global consensus on a simple definition of CKD - kidney damage or a GFR < 60 ml/min/1.73 m^2 for 3 months or more, irrespective of cause (Levy, Morgan et al. 2004). Depending on GFR the CKD is classified into five stages of which the fifth one is known as ESRD. Description of those stages together with GFR values are presented in Table 2.1.

Table 2.1 Stages of CKD. Source: (Levey, Eckardt et al. 2005)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>ml/min/1.73m^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or increased GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mildly decreased GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Renal failure</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>

The ESRD is a condition with established renal failure, when GFR<15ml/min/1.73m^2. It is possible to lose as much as 90% of kidney function without experiencing any symptoms or problems. Dialysis for acute renal failure is not considered as ESRD unless renal function fails to recover.

2.2.1 Causes of ESRD

The ESRD is caused primarily by renal diseases, such as glomerulonephritis, pyelonephritis and polycystic, diabetic, hypertensive and renovascular kidney disease (Chambers, Brown et al. 2010).

Kramer et al. (2009) performed a study on changes in primary renal disease of European ESRD patients for the period 1997-2006. The study is based on the data obtained from national registries of 19 countries, which included Austria, Denmark, England/Wales [United Kingdom (UK)], Finland, Greece, Iceland, Norway, Scotland (UK), Sweden, The Netherlands and the regional registries of Dutch- and French-
speaking Belgium, Calabria (covering 4% of Italy) and Andalusia, Asturias, Basque country, Cantabria, Catalonia and Valencian region (covering altogether 53% of Spain). The results of this research showed that for the studied period the age- and gender-adjusted incidence rates of patients starting the treatment due to glomerulonephritis/sclerosis and pyelonephritis have decreased, while the rates of patients starting the treatment due to polycystic kidneys remained stable (Figure 2.2).

![Figure 2.2 Trends in the incidence of ESRD pmp and average annual percentage change (95% confidence interval), during the period 1997–2006, by primary renal disease, adjusted for age and gender distribution. DM: diabetes mellitus; GN: glomerulone nephritis/sclerosis; HT/RVD: hypertension/renal vascular disease; Misc: miscellaneous; PKD: polycystic kidneys, adult type; PN: pyelonephritis; Unkn: unknown/missing. Source: (Kramer, Stel et al. 2009) The figure is reproduced with the kind permission of the publisher, ©Oxford University Press.](image)

After a long period of increase, the incidence rates of patients on RRT due to hypertension/renal vascular disease or miscellaneous causes started to stabilize in 2004, whereas those due to ‘unknown/missing’ causes continued to rise. Incidence of ESRD due to diabetes till the year 2000 had a continuous increase, whereas after 2000 the increase was equal to half of the previous rates (i.e. before 2000). Additionally, analysis per age group performed by the authors showed that changes in the incidence rates of ESRD patients due to diabetes or hypertension/renal vascular disease were explained by changes of the incidence rates due to these causes in the age groups 65-74 and 75-84 years (Kramer, Stel et al. 2009).
The full spectrum of diseases documented as leading causes for dialysis initiation throughout Europe is summarized in Figure 2.3.

Figure 2.3 The full spectrum of diseases that are documented as leading causes for dialysis initiation throughout Europe. Outside the circle the major renal diseases are presented. Numbers in parentheses represent number of patients. Source: (Wanner 2011). The figure is reproduced with the kind permission of the author.

The data are presented by the Working Group on Inherited Kidney Disorders. This group is officially recognized as ERA-EDTA Working Group. The working group takes into account the wide diversity of the inherited kidney disorders area,
including the adult and paediatric nephrology, and the clinical, research, genetics, physiology and pathophysiology aspects (ERA-EDTA 2011).

2.2.2 Co-morbidities in patients with ESRD

Morbidity is a diseased state, disability, or poor health due to any cause. Co-morbidity, in its turn, describes the effect of all other diseases an individual patient might have other than the primary disease of interest.

Table 2.2 Summary of co-morbidity of incident ESRD patients provided by selected national renal registries. UK RR: United Kingdom Renal Registry. Source: (Chambers, Brown et al. 2010)

<table>
<thead>
<tr>
<th>National registries</th>
<th>ANZDATA</th>
<th>USRDS</th>
<th>UK RR</th>
<th>Necosad 2****</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1953</td>
<td>696 043</td>
<td>15 197*</td>
<td>1041</td>
</tr>
<tr>
<td>Ischaemic heart disease incl. MI</td>
<td>30.5%</td>
<td>23.8%</td>
<td>24.1%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>11.0%</td>
<td>9.0%</td>
<td>11.7%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>19.0%</td>
<td>14.3%</td>
<td>14.2%</td>
<td>13.0%</td>
</tr>
<tr>
<td>COPD</td>
<td>12.0%</td>
<td>7.1%</td>
<td>7.7%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Diabetes**</td>
<td>35.0%</td>
<td>41.2%</td>
<td>18.8%</td>
<td>19.5%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>not collected</td>
<td>5.3%</td>
<td>11.5%</td>
<td>10.1%</td>
</tr>
<tr>
<td>Smoking</td>
<td>11.0%</td>
<td>5.2%</td>
<td>18.4%</td>
<td>not collected</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>not collected</td>
<td>32.0%</td>
<td>not collected</td>
<td>12.3%</td>
</tr>
<tr>
<td>Patients with no co-morbidity at start of RRT***</td>
<td>39.0%</td>
<td>9.4%</td>
<td>38.7%</td>
<td>not collected</td>
</tr>
</tbody>
</table>

Notes: *Comprehensive co-morbidity information was only available in 5916 patients. **Countries may sometimes include those patients who were diabetic, but their disease was not a primary cause of renal failure in this total. ***U.S. data includes hypertension (74%) and also congestive cardiac failure as a co-morbidity. COPD: chronic obstructive pulmonary disease. ****Necosad stands for: Nederland’s Co-operative Study Adequacy of Dialysis (treatment). It is an extensive scientific research project financed by the Kidney Foundation and the government. Necosad started in 1993, as a two-year feasibility study of 250 patients from 13 centers, and was financed by the Dutch Kidney Foundation (NECOSAD).
Co-morbidities are increasingly common in new patients with ESRD; 34% have heart failure, 25% coronary artery disease, 16% peripheral vascular disease, 10% cerebrovascular disease or previous cerebrovascular accident, 30% diabetes, 10% chronic obstructive pulmonary disease, and 7% cancer. In the UK, 18% of patients with ESRD have diabetes, compared with 25% in Australia, 36% in Germany, and 44% in the U.S. (Levy, Morgan et al. 2004). In general, patients with ESRD carry a significantly higher cardiovascular morbidity compared to the general population (Blakeley 2008).

The summary of co-morbidity of incident ESRD patients collected from selected national registries, such as Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), United Kingdom Renal Registry, USRDS and Necosad-2 study is presented in Table 2.2. It can be seen from the table that ischaemic heart disease and diabetes are the major co-morbidities in patients starting treatment independently of their residence country.

### 2.3 RENAL REPLACEMENT THERAPY AND RENAL TRANSPLANTATION

Renal replacement therapy is a term used to encompass life-supporting treatments for renal failure; these include HD (in center or at home), PD, either Continuous Ambulatory Peritoneal Dialysis (CAPD) or Continuous Cyclic Peritoneal Dialysis (CCPD) and RTx. Basic knowledge on RRT can be found in several textbooks (Kasper, Braunwald et al. 2004; Blakeley 2008; Chambers, Brown et al. 2010).

The first HD in a human was undertaken by George Hass in 1926 with a fatal outcome. It took 19 years before the first successful HD was performed in 1945 by Kolff for acute renal failure. It was only through the development of the arteriovenous shunt in the early 1960s that the outlook changed also for patients with CKD. The first successful RTx involved a kidney transplant between identical twins, was performed by Joseph Murray and was successful because no immunosuppression was necessary in genetically identical twins. RTx only became more successful once graft rejection could be effectively countered with the introduction of the effective immunosuppressant ciclosporin in 1983. Finally, the first PD was also performed in a...
human in 1926 by Georg Ganter, though it became established as a mode of therapy for CKD in the 1980s.

There are two basic principles of dialysis that allow the body’s homeostasis to be achieved in the absence of a natural kidney. They are as follows:

- **Convection**, in which there is movement (in large volumes) of solvent, which drags dissolved solute across a membrane with a hydrostatic pressure gradient.

- **Diffusion**, in which there is passive movement of solute from a high- to a low-concentration gradient across a membrane. Diffusion depends not only on the transmembrane gradient but the membrane characteristics as well (e.g., pore size).

Diffusion is more effective in clearing small molecules and convection improves mid-size molecule clearance.

Many HD techniques have been developed, particularly in the intensive care unit setting, ranging from conventional HD, high-flux HD, hemodiafiltration, and hemofiltration. These techniques simply use varying degrees of convection or diffusion.

The HD procedure is targeted at removing both low- and high-molecular-weight solutes (Figure 2.4). The procedure consists of pumping heparinized blood through the dialyzer at a flow rate of 300 to 500 mL/min, while dialysate flows in an opposite counter-current direction at 500 to 800 mL/min. The clearance of urea ranges from 200 to 350 mL/min, while the clearance of 2 microglobulin is more modest and ranges from 20 to 25 mL/min. Dialysis adequacy is measured by urea kinetic modeling using the urea reduction ratio, or Kt/V, where K is the dialyzer urea clearance, t is the duration of dialysis, and V is the urea distribution volume. In a well-nourished stable HD patient, a Kt/V of 0.8 to 1.0 is the minimum acceptable threshold per dialysis session. The dose of dialysis, which is defined as the magnitude of urea clearance during a single dialysis treatment, is further governed by patient size, residual renal function, dietary protein intake, the degree of anabolism or catabolism, and the presence of co-morbid conditions.

Much debate surrounds the “optimal” dialysis dose, although a minimal dialysis dose has been universally accepted. For the majority of patients with ESRD, between
9 and 12 h of dialysis is required each week, usually divided into three equal sessions. However, the dialysis dose must be individualized. Hemodialysis can be performed at home or in the hospitalization center.

![Diagram of patient connected to the HD machine](http://goeshealth.com/family-health/hemodialysis-patients-moral-support-family.html/attachment/hemodialysis)

**Figure 2.4 Schematic diagram of patient connected to the HD machine.** HD uses a special filter called a dialyzer. During treatment, blood travels from the body through tubes into the dialyzer, which filters out wastes and extra water. Then the cleaned blood flows through another set of tubes back into the body. The dialyzer is connected to a machine that monitors blood flow and disposes of the wastes. Picture’s source: [http://goeshealth.com/family-health/hemodialysis-patients-moral-support-family.html/attachment/hemodialysis](http://goeshealth.com/family-health/hemodialysis-patients-moral-support-family.html/attachment/hemodialysis)

Home hemodialysis consists in providing ESRD patients with HD at home. Depending on the duration and frequency of sessions, HHD is divided in types as follows:

1. Conventional HHD is done three times a week for three to four hours or longer each time.

2. Short daily HHD is usually done five to seven times a week using new machines designed for short daily home treatment. Treatments usually last about two hours each.
3. Nocturnal HHD is done at night while the patient sleeps. It may be done six nights a week or every other night. Treatments usually last about six to eight hours.

The most common HD related complications are: hypotension, anaphylaxis, catheter-related sepsis, pyrogenic reactions, dialysis equilibrium syndrome, while modern fail-safe machines minimizing other complications such as air embolism and accidental disconnection (Blakeley 2008).

![Diagram of PD](http://anp-renal-failure.blogspot.com/2010/06/peritoneal-dialysis.html)

Figure 2.5 Schematic diagram of PD. The process uses the patient's peritoneum in the abdomen as a membrane across which fluids and dissolved substances (electrolytes, urea, glucose, albumin and other small molecules) are exchanged from the blood. Fluid is introduced through a permanent tube in the abdomen and flushed out either every night while the patient sleeps (APD) or via regular exchanges throughout the day (CAPD). Picture’s source: [http://anp-renal-failure.blogspot.com/2010/06/peritoneal-dialysis.html](http://anp-renal-failure.blogspot.com/2010/06/peritoneal-dialysis.html)

In PD, patient’s peritoneum in the abdomen is used as a natural semipermeable membrane across which fluids and dissolved substances are exchanged from the blood. Dissolved waste products and water pass from the blood, via the peritoneal capillaries, through the mesothelial cells and interstitium to the PD fluid (Figure 2.5). Water-soluble waste products pass down a concentration gradient that is generated by an osmotic gradient.
PD regimens are all based on repetitions of a basic cycle, which comprises inflow of PD fluid, a dwell time of the PD fluid within the peritoneal cavity, and then drainage. The various types of PD are all based on this principle. They include CAPD, Automated Peritoneal Dialysis (APD), commonly referred to as CCPD, tidal PD, and intermittent PD. In CAPD, dialysis solution is manually infused into the peritoneal cavity during the day and exchanged three to four times daily. A nighttime dwell is frequently instilled and remains in the peritoneal cavity through the night. The drainage of spent dialysate is performed manually with the assistance of gravity to move fluid out of the abdomen. In CCPD, exchanges are performed in an automated fashion, usually at night; the patient is connected to the automated cycler, which then performs four to five exchange cycles while the patient sleeps. PD cyclers automatically cycle dialysate in and out of the abdominal cavity.

Although PD is a technically safe procedure, there may be clinical reasons to convert to temporary HD. The most usual PD-related complications are: abdominal surgery, diaphragmatic fluid leak resulting in effusions, respiratory compromise from splinting of diaphragm by PD fluid, severe hypoalbuminemic state, peritonitis or catheter-related sepsis, inadequate ultrafiltration in the context of aggressive fluid management and/or hypercatabolic state of the patient.

Kidney transplantation or renal transplantation involves in placing a healthy kidney into the body of a patient with ESRD. A kidney transplant is placed in the human lower abdomen, where it is surgically connected to nearby blood vessels and the bladder (Figure 2.6). The vein and artery of new kidney are attached to the patient’s vein and artery. The new kidney's ureter is attached to the bladder to allow urine to pass out of the body. In most cases, the diseased kidneys are not removed.

Typically, RTx is classified as deceased-donor (formerly known as cadaveric) or living-donor RTx depending on the source of the recipient organ. Cadaveric kidneys may be either from patients with brainstem death and a maintained cardiac output or from nonheart-beating donors. Donors with sepsis, malignancy, infection with hepatitis B, hepatitis C, HIV, or tuberculosis, or irreversible renal failure are not considered for donation.
Figure 2.6 A kidney transplant is placed in human lower abdomen. Source: The Cleveland Clinic Foundation (http://my.clevelandclinic.org/) with the permission.

The use of kidneys from living donors is recommended for RTx whenever possible, in light of the growing evidence of favorable outcomes after RTx. Before being selected as a living donor, thorough counseling, medical, physical, and psychological evaluation is performed. Outcome studies have revealed lower mortality rates in living donors compared with the general population. This is probably caused in part by patient selection and the fact that this group of patients receives long-term medical follow-ups.

There are few absolute contraindications to RTx. These are uncontrolled cancer, HIV positivity, active systemic infections, and/or any condition with a life expectancy of shorter than two years. Conditions increasing the risk of post transplant morbidity and mortality include long duration of dialysis, previous incidence of recurrent infections, cardiovascular disease, and gastrointestinal complications. Such patients require a particularly careful work-up and aggressive management of risk factors (e.g., hypertension, obesity, and vascular disease) before RTx.

The immunosuppression regime is tailored to each patient in an effort to minimize rejection as well as side effects. The commonest regime is triple therapy, e.g., cyclosporin, azathioprine, and prednisolone.

There are three time-dependent types of complications of RTx: immediate, early and late. Acute tubular necrosis and surgical complications are the most common immediate complications for RTx. Surgical complications include renal vein and
arterial thrombosis and urinary leaks. The early complications of RTx are acute rejection due to rise in serum creatinine, infection complications, or mechanical complications, such as arterial and ureteric stenoses and lymphoceles exerting local pressure. Chronic rejection due to a combination of immunological and nonimmunological factors, recurrence of original disease, cardiovascular disease and malignancy (particularly skin cancer) are late complications of patients with RTx.

Kidney transplant represents the best mode of therapy for ESRD patients, both in terms of cost-effectiveness and QOL (Evans, Manninen et al. 1985). There have been many improvements in RTx, such as the refinement of immunosuppression regimens, and patient-donor selection and work-up. The major challenge remains independently of the country: RTx demand far outstrips the organs’ availability. Effort should be made towards the increase of the number of donors. In parallel, there is much research in the development of stem cell RTx and xenotransplantation.

2.4 INCIDENCE AND PREVALENCE

In epidemiology, there are two basic measures of the amount of the disease in population, namely prevalence and incidence.

The incidence of a disease is the number of new cases occurring in a particular time period, such as one year. The incidence rate is therefore the ratio of new cases of the disease to the total number of people at risk:

\[
\text{Incidence rate} = \frac{\text{number of new cases of the disease}}{\text{total number of people at risk during a specific time period}}
\]

The prevalence of a disease is the number of people affected by it at a particular moment in time. The prevalence rate is therefore the ratio of the number of people with the disease to the total number of people at risk:

\[
\text{Prevalence rate} = \frac{\text{number of cases of the disease at a particular time}}{\text{total number of people at risk at a particular time}}
\]
Incidence and prevalence rates are most often stated in pmp (Essex-Sorlie 1995).

Prevalence on one side reflects the status of disease in a population at some point in time (e.g. end of the year), and on the other side provides an estimate of chances for an individual in the population to be ill at some point in time.

The term incident patients refers to the number of the new coming patients during a specified period of time, while prevalent patients is the number of those who are on treatment at a specified time.

The adjusted incidence or prevalence rates are derived applying the weights of a reference population to the observed variable-specific rates (e.g. incidence rate per age group) in a country. This weighed average provides for each country a single summary rate that would be expected if that country had the age and gender distribution of the reference population (ERA-EDTA).

The three largest renal dialysis and transplant registries archiving information on ESRD incident and prevalent patients’ numbers are:

- The USRDS (collects data on >90% of all patients undergoing dialysis in the U.S.).

- The ERA-EDTA; data voluntarily supplied from units in 40 countries across Europe; 70% of the patients live in France, Germany, Italy, Spain, or the UK.

- The ANZDATA; contains data on all patients in Australia and New Zealand who have received dialysis or a transplant since 1980.

The data from ERA-EDTA and USRDS reports were used during the implementation of the projection model and the elaboration of the current thesis.
Chapter 3
ESRD EPIDEMIOLOGY AND PATIENTS’ QUALITY OF LIFE

3.1 ESRD EPIDEMIOLOGY WORLDWIDE

3.1.1 Incidence

Incidence rates of ESRD across the globe show different trends: rates have decreased in some countries, while they have risen or remained stable in others. In 2009, the U.S. unadjusted incidence was the second highest (371 pmp) behind Mexico. Rates were slightly lower in Taiwan and Japan (around 300-350 pmp) and substantially lower in Western Europe (about 80-150 pmp) (USRDS 2011). These rates are presented in Figure 3.1. Despite being second in the world by incidence rates, U.S. has been reported to have slowing rates of new ESRD patients starting the treatment (Nissenson and Fine 2008).

The latest report by Kramer et al. (2009) has shown either continuous increase or stabilizing trends in incidence in Europe. In this report data from 19 European
countries were analyzed for the period 1997-2006 (for the list of countries that participated in the study please refer to the subchapter 2.2.1). In half of these countries there has been an increasing trend, while in the other half the trend is decreasing. The total adjusted incidence rate of ESRD in these countries increased from 109.9 pmp in 1997 to 119.7 pmp in 2000, i.e. an average increase of 2.9% per year. Thereafter, the adjusted incidence rate increased more slowly to 125.4 pmp in 2006 (Kramer, Stel et al. 2009).

The incidence of ESRD is often influenced by a combination of different factors. These factors include risk factors for CKD, progression from CKD to ESRD, cardiovascular disease, late referral to nephrologist, general state of patients’ health (smoking, diabetes etc.) and ethnicity.

The large differences in ESRD incidence between Germany and England and Wales (193.0 per million of the adult population in Germany and 107.5 pmp in adults in England and Wales) were compared in a study by Caskey et al. (2006). The authors explained much of the difference in ESRD incidence by a greater prevalence of diabetes, hypertension, and vascular disease in the German general population, particularly in people older than 65 years, and lower competing mortality risk (Caskey, Schober-Halstenberg et al. 2006). In contrast to this study, Kramer et al. (2009) has reported that especially in older age groups the incidence rates in Europe showed flattening due to diabetes and hypertension, despite the latest steady increase of these diseases in general population (Kramer, Stel et al. 2009). The authors suggested that this could be due to increasing awareness of the burden of CKD and greater emphasis given to early detection and prevention (Kramer, Stel et al. 2009; Zoccali, Kramer et al. 2009). Pharmacological approaches aim to decrease risk of progression to CKD and - in case of failure - to minimize the risk of progression from CKD to ESRD (Devins, Mendelssohn et al. 2003; Meguid El Nahas and Bello 2005).

As demonstrated in earlier studies, differences in nephrologists’ and physicians’ judgment on patients suitability for dialysis over the two last decades is no longer considered to be a major reason for variation in ESRD incidence rates from country to country (Challah, Wing et al. 1984; Parry, Crowe et al. 1996; McKenzie, Moss et al. 1998). Among other factors influencing differences in ESRD incidence rates are the prevalence of early CKD stages, the rate of progression, the influence of competing mortality and the indications for starting ESRD treatment as well as the availability of such treatment (Hallan and Vikse 2008). Ethnicity is another key factor, and one that
is likely to become increasingly important over the next decade. Black patients have
greater mortality and risk of developing ESRD in all cohorts, though black patients
with ESRD have lower risk of death than white patients with ESRD (Hsu, Lin et al.
2003). In the U.S. black patients with hypertension or diabetes are 2-3 times more
likely to develop ESRD than their white counterparts (Xue, Eggers et al. 2007); rates
3-4 times higher than these in the white population have been observed in blacks and
Indo-Asians in the UK (Roderick, Raleigh et al. 1996).

The phenomenon of recent decline in incidence increase could be explained by
several factors, among which are stabilization in the prevalence of underlying causes
of ESRD, slower progression from CKD to ESRD and higher mortality in early stages
of CKD (Kramer, Stel et al. 2009).

3.1.2 Prevalence

Despite remarkable progress in slowing the growth of the number of new ESRD
cases, the prevalent populations continue to grow, mainly because of a reduction in
mortality.

In Europe, the prevalence of ESRD was reported to have slower increase during
the period 2000-2006 in comparison with the period 1997-2000. This is valid for most
European countries, while in Calabria (Italy), Catalonia (Spain), Denmark and
Valencia region (Spain) it appears that prevalence has stabilized. The overall
prevalence increased from 641.6 pmp in 1997 to 815.6 pmp in 2006, with an average
annual increase of 2.7% (Kramer, Stel et al. 2009).

In 2009 almost double prevalence rates of U.S. compared to Western Europe
brought the country in the third place by prevalence in the world after Taiwan and
Japan. The lowest unadjusted rates in prevalence in Europe were reported for Russia,
Romania and Luxembourg (Figure 3.2).

Kramer et al. (2009) has reported on trends in European ESRD prevalence by
type of therapy. Between 1997 and 2006, the adjusted prevalence of patients receiving
HD increased from 301.0 to 376.2 pmp with an average annual increase of 1.9% per
Figure 3.2 Prevalence of ESRD in 2009. Unadjusted prevalence rates pmp. Data for Belgium & England/Wales/Northern Ireland do not include patients younger than 20 & 18, respectively. Data for France include 13 regions in 2005, 15 regions in 2006, 18 regions in 2007, & 20 regions in 2008 & 2009. Source: (USRDS 2011)
The prevalence of patients with a functioning kidney transplant increased from 275.6 to 362.5 pmp having a 3.1% annual increase during the years 1997-2006. The prevalence of patients on PD increased from 59.1 in 1997 to 69.8 pmp in 2000 with a 5.5% p.a. increase, and stabilized thereafter during the period 2000-2006 with an annual increase of 0.4% \((\text{Kramer, Stel et al. 2009})\).

Continuous increase of prevalence could be reduced by addressing prevention strategies for further reduction of ESRD incident rates in order to ease the disease burden in the ESRD prevalent population \((\text{Nissenson and Fine 2008})\).

### 3.1.3 Treatment modality

Hemodialysis continues to be the most common mode of therapy worldwide, evidenced by data showing that, in over 70% of countries reported in the USRDS report concerning the year 2009, at least 80% of patients are on this mode of therapy. In Hong Kong and Mexico, in contrast, PD is used by 78% and 58.5% of patients, respectively. Luxembourg has the highest use of in-center HD, at almost 99%. The highest percent of provided HHD is 16.3% and 9.3% in New Zealand and Australia, respectively \((\text{USRDS 2011})\).

The choice between HD and PD involves the interplay of various factors that include the patient’s age, the presence of co-morbid conditions, the ability to perform the procedure, and the patient’s own conceptions about the therapy. PD is favored in younger patients because of their better manual dexterity and greater visual acuity, and because younger patients prefer the independence and flexibility of home-based PD treatment \((\text{Kasper, Braunwald et al. 2004})\). Younger patients (<20 years old) have a far greater representation in the PD population with about 40% of the reported countries (including the U.S.) using CAPD and CCPD. With increasing age, there is a reduced utilization of PD - particularly in older patients. Regardless of age, however, Australia, New Zealand, and Denmark maintain the highest utilization rates of both home CAPD/CCPD therapy compared to any other country \((\text{USRDS 2011})\). Larger patients (i.e. above 80 kg of bodyweight), patients with no residual renal function, and patients who have truncal obesity with or without prior abdominal surgery may be more suited to HD \((\text{Kasper, Braunwald et al. 2004})\).
Figure 3.3 Transplant rates in 2009. Unadjusted transplant rates pmp. Data for Belgium & England/Wales/Northern Ireland do not include patients younger than 20 & 18, respectively. Data for France include 13 regions in 2005, 15 regions in 2006, 18 regions in 2007, & 20 regions in 2008 & 2009. Source: (USRDS 2011)
Commonly accepted criteria for placing patients on dialysis include the presence of the uremic syndrome; the presence of hyperkalemia unresponsive to conservative measures; extracellular volume expansion; acidosis refractory to medical therapy; a bleeding diathesis; and a creatinine clearance of 10 mL/min per 1.73 m$^2$. Early referral to a nephrologist for advanced planning and creation of a dialysis access, education about ESRD treatment options, and the aggressive management of the complications of CKD, including acidosis, anemia, and hyperparathyroidism, are important (Kasper, Braunwald et al. 2004).

Rate of performed transplantations vary from country to country and this is mainly explained by the organ availability (Figure 3.3). The Eurotransplant International Foundation (The Netherlands, Austria, Belgium, Germany, Croatia, Slovenia and Luxembourg) and Scandiatransplant, The Nordic organ exchange organization, (Denmark, Finland, Norway, Iceland and Sweden) have shown decades of successful cooperation of the countries in jointly promoting and organizing transplant activity.

The RTx rate in these countries remains high, while these international organizations keep successfully coping with the RTx increasing demand. A good example of a country with a well established system on kidney transplants allocation starting from the 1990s is Spain. A permanent network of trained medical staff responsible for the organ donation and removal process in all centers accredited for that process had been established and increased significantly organ availability. This resulted in an increase in the donation rate from 14 donors pmp in 1989 to 50 in 2009 (Miranda, Vilardell et al. 2003; USRDS 2011).

### 3.1.4 Survival of ESRD patients

End-Stage Renal Disease is associated with a higher mortality compared to age-matched controls. Generally speaking, the prognosis for some patients on RRT remains poor. For example, a patient over 75 would have a 63% chance of surviving for 1 year after commencing RRT and a 34% chance of remaining alive 3 years after commencing RRT. Older patients with diabetes have considerably lower survival rates than younger patients, but the impact of diabetes on their relative risk of death, compared to younger patients, is much less (Chambers, Brown et al. 2010).
The study by Kramer et al. (2009) for 19 European countries for the period 1997-2006 has shown that the patient survival was very similar for patients who began dialysis between 1997 and 2001 and those who started between 2002 and 2006. However, after adjustment for age, gender, primary renal disease and country, the results showed that the risk of death for the patients who started dialysis during the period 2000–2006 was reduced by 11% compared to those who started in the previous period. The improvement over time was more obvious for patients on PD (19%) than for HD patients (10%) (Kramer, Stel et al. 2009).

The same study presents the results of patients’ survival on RTx. Both patient and graft survival have improved in patients receiving a kidney transplant for the first time. After adjustment for age, gender, primary renal disease and country, the risk of death in the 2002-2006 cohorts was reduced by 17% and the risk of graft failure by 11%. This improvement was more obviously seen in living donor transplants - 30% for patient survival and 9% for graft survival, than in deceased donor transplants - 13% for patient survival and 8% for graft survival (Kramer, Stel et al. 2009).

In the U.S., the overall death rate of dialysis patients has decreased over the last decade to approximately 23 deaths per 100 patient years, despite the increasing age and co-morbidity of patients. Patients that start dialysis between age 15 and 19 have a 80% 10-year survival; those aged 40-49 years a 36% 10-year survival; and those 60-64 years a 10% 10-year survival. Survival is also reported to be increased in American black people. A 50-year-old man starting dialysis in the U.S. could expect to live 5 years if he is a white person, and over 6 years if a black person (longer if transplanted). For a 30-year-old these figures would be 10 and 12 years, and for a 60-year-old 4 and 5 years respectively (Levy, Morgan et al. 2004).

### 3.1.5 Causes of mortality

Mortality is the condition of being subject to death. Mortality rate is a measure of the number of deaths (in general, or due to a specific cause) in a population, scaled to the size of that population, per unit of time.

In all the countries, the major cause of mortality (half of those reported) in patients with ESRD receiving dialysis as treatment is cardiovascular disease. The rate of mortality from cardiac disease is higher in patients on HD compared to that of patients on PD and RTx (Kasper, Braunwald et al. 2004). Infection is the next major
cause (25%) and cerebrovascular disease is the third largest cause of death (6%). One in five dialysis patients withdraws from dialysis before death in the U.S. because of failure to thrive or medical complications. Withdrawal is commoner in older, Caucasian dialysis patients. Withdrawal rates in the U.S. are higher than in most other countries, possibly because of the initial acceptance of patients with marginal benefit from dialysis. In the UK 35% patients die from cardiac disease, 20% from infection, 13% from stopping dialysis, 9% from malignancies, and 7% from cerebrovascular disease (Levy, Morgan et al. 2004).

3.1.6 Advances in ESRD treatment technologies

During the last 60 years, there has been an exciting evolution in the field of dialysis, which has led to important changes in the outcome of ESRD patients. The need to provide dialysis patients with a better QOL has increased the interest in developing new techniques, such as the wearable artificial kidney, although still in initial clinical development (Cavalli, Del Vecchio et al. 2010). Currently ongoing European project, Nephron Plus, aims at the development of the next generation ICT (Information and Communication Technology) enabled Renal Care solution for personalized treatment and management of patients with ESRD. It presents an ideal solution for continuous dialysis outside the hospital environment. It relies on an ICT-enabled wearable artificial kidney for on body blood purification (Nephron+). New directions in dialysis research include cheaper treatments, home based therapies and simpler methods of blood purification. These objectives may probably be obtained with innovations in the field of artificial kidney through the utilization of new disciplines such as miniaturization, microfluidics and nanotechnology. Such research may lead to a new era of dialysis in which the new challenges are transportability and wearability. Recently, interesting and promising results on the application of wearable ultrafiltration systems and wearable artificial kidneys have been published (Ronco, Davenport et al. 2011). However, the hard ongoing work on introducing new technologies together with the improvement of the existing techniques of RRT have not yet eliminated the need of CKD prevention and treatment improvements in order to avoid the progression to ESRD and the need of dialysis itself.

Advances in science of transplantation have lead to outstanding short-term graft and patient survival rates. Despite that, organ transplantation continues to face several major challenges. These include a severe shortage of donor grafts, poor long-term
graft survival resulting from chronic vascular rejection, and major side effects from long-term immunosuppressive therapy required for prevention of rejection. The necessity for the development of novel solutions to those challenges in organ transplantation has been stressed. The increase of availability and quality of organs for transplantation may reduce patient death while on the waiting list and facilitate long-term graft survival after transplantation. Further understanding of the molecular mechanisms of cell activation has led to the discovery of additional new immunosuppressive agents that may be used to allow individualization of immunosuppressive therapy. New strategies for monitoring the use of immunosuppressive agents could reduce the incidence and severity of renal and cardiovascular toxicity and the increased incidence of cancer in transplant patients (Levy 2010).

3.2 QUALITY OF LIFE OF ESRD PATIENTS

Therapy options for ESRD patients include either life sustaining dialysis or the only treatment method, kidney transplantation. Both ways of therapy greatly affect QOL of the patients (Valderrabano, Jofre et al. 2001; Fukuhara, Lopes et al. 2003). Health-related quality of life (HRQOL) is a measure of well-being of ESRD patients and an independent prognostic predictor. Patients on RRT or those living with kidney transplant encounter many physical, psychological, and social stress factors that lead to a decrease in their QOL. Physical complaints frequently identified by dialysis patients include muscle, bone and joint aches, sleep disturbances, itchy/dry skin, gastrointestinal upsets, difficulty concentrating, cough and shortness of breath, headaches, decreased sexual function, cramps and dizziness (Laupacis, Keown et al. 1996). Most of these symptoms are ameliorated in patients who receive a functioning transplant, although other physical symptoms may be induced by necessary immunosuppressive medications (Laupacis, Keown et al. 1996). Greater age and co-morbidity burden, particularly anaemia, intermittent claudication and diabetes, have been shown to associate with worse physical functioning (Moreno, Lopez Gomez et al. 1996).

Psychosocial effects of dialysis treatment extend to family, partners and friends of the patient who are often required to limit their own activities to assist and care for the patient. Socioeconomic factors affecting RRT patients’ QOL include unemployment, low education, low income, home management and recreation
(Moreno, Lopez Gomez et al. 1996; Valderrabano, Jofre et al. 2001). Among psychological factors associated with lower QOL are depression and anxiety.

Employment of patients on RRT is associated with better QOL and lower depression scores (Araujo, de Bruin et al. 2011). Kutner et al. (2010) investigated how depressed mood and activity level affected patients' employment after starting dialysis. The number of patients who had depression was almost three times higher among no employed patients compared to patients who kept working after starting dialysis. Based on the study authors come to the conclusion that management of depressive symptoms and support for increased activity level may facilitate patients' opportunity for continued employment after dialysis start, along with generally improving their overall QOL (Kutner, Zhang et al. 2010). Employment status at the time of RTx and in post-transplant period has a strong and independent association with the graft and recipient survival. Full time employment at the time of transplantation and at one-year post-transplant is associated with lower risk for graft failure and recipient mortality. However overworking might be associated with potential risk for graft survival (Petersen, Baird et al. 2008).

Compared to HD, the RTx provides significantly higher QOL to ESRD patients (Evans, Manninen et al. 1985; Rambod, Shabani et al. 2011). Landreneau et al. (2010) has made an attempt to determine the size of effect of RTx on patients’ QOL when compared with HD. The analysis of sixteen studies has lead to the following conclusions: compared to hemodialysis, renal transplantation was the most effective in improving general overall QOL (0.98 effect size), less improving physical functioning (0.77 effect size) and least improving psychological functioning (0.39 effect size) (Landreneau, Lee et al. 2010).

PD and HHD are conducted in patient’s home environment. The latest study on dialysis mode effectiveness performed by Thodis and Oreopoulos (2011) revealed that PD showed better outcomes compared to CHD for the first 2-3 years and HHD showed better outcomes for the long-term. Either type of dialysis offers a high QOL and a high degree of independence to the RRT patients. Based on their finding, the authors of the study suggest that HHD should be more often proposed as first type of treatment for the new coming patients, instead of being given a choice between HD or PD treatment (Thodis and Oreopoulos 2011).

Two PD dialysis types, APD and CAPD, were compared by Balasubramanian et al. (2011) on UK patients with ESRD. A single-centre retrospective study of incident
patients initiating APD and CAPD with data collected prospectively over 5 years was performed. PD modality was based on patient preference. Health status was assessed using SF-36 (for the term details please refer to the Appendix A) questionnaires at initial and 1-year follow-up appointments. The results have shown that generally CAPD patients were older and more dependent than APD patients. Univariate analysis for technique survival was inferior for CAPD (relative risk for failure 1.46). But on multivariate analysis when co-morbidity was added into the model, PD was no longer a significant predictor of technique survival. There was no difference in decline in residual renal function. In comparison with APD patients, CAPD patients had worse health status; mean physical scores were 36.5 versus 32.3 and social composite scores were 40.3 versus 33.3, respectively. After 1 year, health status scores for CAPD and APD patients were similar. This study did not show any advantages of APD over CAPD in terms of technique survival or health score. There is no evidence to support one PD modality over the other and both types of therapy should be available to allow patient choice (Balasubramanian, McKitty et al. 2011).

Studies investigating whether the HRQOL in HD patients have improved over a ten year period have shown contradictory results. A study by Mazairac et al. (2011) in the Netherlands has shown significant improvement in HRQOL in HD patients in 2006 Convective Transport Study than in 1995 (NECOSAD-I) in four domains of the SF-36: bodily pain, vitality, role-emotional functioning and mental health, after adjusting for demographic variables. This increment is partly explained by the authors by improved haemoglobin and phosphate levels. Compared to the general population, HRQOL improvement was most outspoken in two domains: bodily pain and role-emotional (Mazairac, de Wit et al. 2011). On the contrary, a similar study, based on data on 11,079 U.S. patients subjected to SF-36, has shown that physical functioning, general health, vitality, social functioning, and physical component summary scores were unchanged among patients over the study period from 1997 to 2006 (Gabbay, Meyer et al. 2010).

The reasons for worse QOL in women with ESRD relative to men are not understood, but it is believed that they are related to psychosocial rather than physical factors (Valderrabano, Jofre et al. 2001). Particularly, straight dependence of lower HRQOL scores in women with higher depression rates has been observed (Alavi, Aliakbarzadeh et al. 2009; Araujo, de Bruin et al. 2011).
The presence of depression has also been found to be associated with increased morbidity and mortality amongst ESRD patients, and may affect compliance of patients to medical treatment (Tossani, Cassano et al. 2005). Furthermore, presence of diabetes, hypoalbuminemia, low education, and pruritus are significantly associated with depressive symptoms. Depressive symptoms are also independently associated with RRT patients’ poor quality sleep (Araujo, de Bruin et al. 2011). It has been already discussed that RTx is associated with much better HRQOL compared to HD. Depression and anxiety are respectively more prevalent in HD patients than in patients living with functioning graft (Alavi, Aliakbarzadeh et al. 2009).

Age is an important parameter to be considered when dealing with ESRD patients’ QOL. Despite having a greater burden of co-morbidity and social problems, elderly patients’ relative QOL gain is better than that of younger HD patients. One study found that the mental health-component score of the SF-36 was almost the same in elderly dialysis patients as in the age-specific general population (Lamping, Constantinovici et al. 2000). For older ESRD patients QOL is particularly important, particularly when likely survival is short (Brown 2010). A comparison of QOL of elderly patients on HD versus PD has shown that those on PD have less illness intrusion. This evidence suggests that there is a room for improving elderly patients QOL by changing the common practice of placing the majority of older patients on HD (Brown 2010; Brown and Johansson 2011). Providing elderly patients with kidney graft instead of HD contributes to the recipients’ reduction in mortality rate and improved QOL as compared to patients on HD and younger kidney transplant recipients (Huang, Segev et al. 2009).

3.3 COSTS OF ESRD PATIENTS’ TREATMENT

The importance of the RRT and RTx costs assessment has been motivated by the increase of ESRD patients’ number, ageing population and improvements in healthcare technology. After novel treatment options for the ESRD patients’ were introduced together with the improvements in existing technologies (e.g., by the introduction of human leukocyte antigen type matching or new immunosuppressive drugs), the survival patterns and the costs associated with treatment had changed, thus leading to the reconsideration of the patients’ modalities assignment management. On one hand, the combination of the demand for renal grafts exceeding the supply and the expanded pool of patients fitting the criteria for receiving a kidney transplant has
led to an increased waiting list. On the other hand, due to their medical condition not all ESRD patients have the option of a more cost-effective treatment modality. All these factors have added the complexity and uncertainty to the health policy decision making.

Worldwide governments allocate a significant proportion of their healthcare budget for the treatment of ESRD patients. For example in 1994 the UK, Germany and France spent 0.7%, 1.3% and 1.5% of their health care budget on dialysis, despite dialysis patients comprising 0.02%, 0.05% and 0.04% of these populations respectively (De Vecchi, Dratwa et al. 1999). In year 2000 Greece was reported to consume 2% of the countries healthcare budget providing treatment to 0.05% of the population (Kaitelidou, Ziroyanis et al. 2005).

Different countries show different figures for dialysis and RTx costs. An important factor is that ESRD funding is “health care system specific”. In countries where health care is publicly provided, direct expenditure on ESRD treatment programs relate to actual costs. In countries where the health care system incorporates a mix of public and private providers, direct expenditure on ESRD treatment is determined by reimbursement figures. The term “costs”, is only applicable to countries with global budgets, where costs have been determined via detailed surveys. “Reimbursements” is used for countries where various modalities are defined by a specific price which is at least equivalent to the actual cost of each modality. For these reasons, De Vecchi et al. (1999) in their attempt to compare ESRD treatment costs between countries (Canada, UK, Denmark, Sweden, Norway, Finland, Spain, Italy, France, Germany, Belgium, The Netherlands, Austria, Japan, Switzerland, USA) had come only to the comparison of trends rather than actual cost estimates (De Vecchi, Dratwa et al. 1999).

ESRD patients’ treatment programs may be categorized by relation to treatment sites – public hospital centres, private centres, limited care centres and homes – as well as to treatment modalities: CHD, Limited Care Hemodialysis (LCHD), which is HD with limited nurse attendance), CAPD and APD. During the comparison of the costs and reimbursements of treatment modalities in different countries, De Vecchi et al. (1999) reported that trends were similar. The costs were the highest for public CHD, followed by private CHD. They were lower on LCHD and the lowest for HHD and CAPD, which were at nearly the same level. The cost level for APD was almost the same as that of LCHD (De Vecchi, Dratwa et al. 1999). The results of the more recent study by Just et al. (2008) are in agreement to the De
Vecchi et al. (1999) conclusions. PD, particularly CAPD, was reported to be a lower cost modality than non-home hemodialysis. The expense to payers for dialysis therapy declined in the following order: most expensive was CHD, then came LCHD costs which are similar to APD, and finally, the lowest were the home-care modalities, CAPD and HHD (Just, Riella et al. 2008).

Winkelmayer et al. (2002) has calculated cost-effectiveness ratios of ESRD treatment modalities based on 13 articles published between 1968 and 1998. According to this review the CHD costs were estimated on average between $55,000 and $80,000 per Lifeyear (LY) gained. The ratios for HHD showed a similar pattern when compared to CHD, with the majority of cost-effectiveness ratios being between $33,000 and $50,000 per LY gained over time. The cost-effectiveness ratios for RTx tended to diminish over time and reach a plateau at approximately $10,000 per LY gained. Furthermore, in all cases where RTx from living donors was assessed separately from cadaveric organs, having a living donor was more cost-effective, and the decreasing trend over time was present as well (due to the reduced costs for the supportive therapy after the surgery). For the case of CAPD, there were not enough data to draw any reasonable conclusions (Winkelmayer, Weinstein et al. 2002).

It is universally agreed that RTx is the cheapest and most cost-effective form of treatment of ESRD patients, and that it is limited by the donor organs availability (Winkelmayer, Weinstein et al. 2002). Improvements in dialysis therapies have resulted in improved patient outcomes, leading to increased survival rates and resulting in increased costs. In contrast, the cost-effectiveness of RTx has been shown to be improving over time (Winkelmayer, Weinstein et al. 2002). In addition, Kramer et al. (2009) in his review has shown that survival rates on PD and RTx were improved during the period 1997-2006. Furthermore, it is generally known that the QOL of transplanted patients is comparable to that of the general population (Evans, Manninen et al. 1985).

The selection of a therapy modality depends to a large extent on the provider's perspective, i.e. being either public or private or having limited HD capacity or overcapacity. Providers in private centres are driven more by the microeconomics of their centres to use the investments maximally for CHD. The CHD requires initial high investments in infrastructure, buildings and personnel. These investments will have to be repaid over a period of time, so that every dialysis station has to be used maximally to refund the investments. In such a system, unused stations not only mean no income but also high fixed costs. Only if capacity limits are reached, the PD
becomes an option. However, “filling up” a CHD programme to full capacity creates another problem: transfer of patients from PD to HD becomes limited and delayed. Thus, maintaining unsuitable patients on PD again increases the costs for the centre. For these reasons, PD tends to be used more commonly in countries with global dialysis budgets \((De \ Vecchi, \ Dratwa \ et \ al. \ 1999)\).

Despite the difficulties in international comparison, the data from Sweden, the UK, the U.S., Italy, Canada, Spain, France, Belgium, Germany and the Netherlands agree that CHD is the most expensive form of dialysis, while HHD and CAPD are the most cost-effective treatment modalities \((De \ Vecchi, \ Dratwa \ et \ al. \ 1999)\). CAPD was determined to be less expensive than HHD in these countries, except Italy. The experience of Japan was reported to be different: PD is reimbursed at a slightly higher rate than HD. In the U.S., there is one reimbursement rate for dialysis patients, and therefore choice of treatment may be driven by the difference between the actual costs of each modality and the reimbursement figure, resulting in higher margins to the provider \((De \ Vecchi, \ Dratwa \ et \ al. \ 1999)\).

### 3.4 PATIENTS WITH ESRD IN GREECE

Several authors have studied different aspects of ESRD treatments in Greece, including patients’ QOL, treatment costs, technology assessment and transplantation outcomes. \(Kaba \ et \ al. \ (2007)\) investigated QOL of ESRD patients’ on HD in Greece. The results of this study were summarized into five major categories describing patients’ experience: problems related to the symptoms, limitations in life, feeling of uncertainty and dependency and changes in personality. Not uncommon to ESRD patients, the studied group of patients marked as problems related to the therapy, fatigue before and after HD. However, in reward for life patients were ready to bear pain, lack of energy, insomnia and heart problems. Limitations of food and fluid intake together with strict diet were the most commonly identified stressor altering the usual lifestyles for most of the patients. Restrictions due to dialysis influence all areas of patients’ life, specifically physical performance, employment, finances and social life. Patients expressed uncertainty related to health instability independently of their state of health at the moment and anxiety about potential problems in future perspective and the prospect of the premature death. On one side, patients stressed strong dependence on life-sustaining “inanimate” technology and, on the other side, secure feeling given by expertise care of the doctors and nurses. Emotionally patients
experienced suicide thoughts or depression, anger and denial as a response to the limitations and restrictions due to dialysis therapy. ESRD patients in Greece are also experiencing difficulties in socializing due to Mediterranean lifestyle, including having coffee and food outside. Not having time or energy to follow their friends, makes dialysis patients feel restricted, isolated, depressed and angry (Kaba, Bellou et al. 2007).

Restrictions due to dialysis have also impact on ESRD patients’ employment status. Kaitelidou et al. (2005) has reported that the majority of ESRD patients in Greece on HD (about 60%) were unable to keep their original profession. Additionally, 36.7% of patients had to retire prematurely, and the (discounted) loss of productivity was estimated at €393.2 million in 2002. Also, 63.6% of employed patients reported absence from work, which resulted in a loss of €7.2 million. Following the initiation of HD, 18.2% of patients needed housekeeping services for an average of 9.1 hours per week, demanding on average 22.7% of their income. It was also found that 9% of the patients had to change their place of residency so that they could be closer to their HD unit, which consequently had an impact on their social lives (Kaitelidou, Maniadakis et al. 2005).

The comparison of HRQOL of patients on HD and PD has shown that the self reported QOL was on average 3.8% and 6.5% higher for the PD patients using the generic part of the questionnaire SF-36 and after incorporating a disease-specific component, KDQOL-SF, (for the term details please refer to the Appendix A) respectively. The same study revealed that in Greece the average annual ESRD patient cost on HD is higher than that on PD by 18.6% (Kontodimopoulos, Niakas et al. 2005).

Economic evaluation of HD treatment in Greece performed based on the prices available in the year 2000, has shown that the total health-sector cost for HD in Greece exceeds €171 million, or €182 per session and €229 per inpatient day. Calculated loss due to mortality was 2,046 years, and the potential productivity cost was estimated at €9.9 million, according to the human capital approach, and €303,000, according to the friction method. Total morbidity cost due to absence from work and early retirement was estimated at more than €273 million, according to the human capital approach, and €12.5 million, according to the friction method. This study came to the conclusion that providing HD care for 0.05% of the population
suffering from ESRD absorbs approximately 2% of total health expenditure in Greece (Kaitelidou, Ziroyanis et al. 2005).

Kontodimopoulos et al. (2008) have conducted a study estimating lifelong costs and Quality-adjusted Life Years (QALYs) of HD, PD and RTx in Greece, based on individual patient life expectancy and using prices available in 2005. A nationally representative patient sample on each modality, HD, PD and RTx, completed the self-administered SF-36 Health Survey, from which the preference-based SF-6D (for the term details please refer to the Appendix A) utility index was derived. Estimated lifelong QALYs were 4.37 (HD), 3.94 (PD) and 16.11 (RTx). Annual HD and PD costs per patient were estimated at €36,247 and €30,719 respectively. For RTx, average 1st year, 3-year and lifelong (undiscounted) costs were €31,714, €43,275 and €151,274 respectively. Cost per QALY was higher in HD (€60,353) compared to PD (€54,504) and 1st year RTx (€45,523). The authors of the study have concluded that HD is used by 75% of the ESRD patients in Greece; the cost-saving efforts must be intensified. Reconsidering supply and reimbursement policies for dialyzers and drugs, establishing satellite dialysis units in remote areas could be explored. Wider use of PD is also in the direction of increasing cost-effectiveness. Finally, efforts are required for disseminating the idea of organ donation (Kontodimopoulos and Niakas 2008).

It is generally accepted that RTx is providing better QOL compared to dialysis treatment for the ESRD patients. Balaska et al. (2006) has evaluated changes in HRQOL in adult patients in Greece one year after successful RTx. For this purpose the SF-36 survey score was used. Eighty-five HD patients, 44 men and 41 women, underwent RT. Thirty-nine patients had received a kidney from a living-related donor, and 46 from a cadaver. The scale scores of a Greek version of the SF-36 survey were compared between the RTx and the HD patients. According to the SF-36 health survey, the transplant recipients had better results for general health perception (P≤0.001), role-physical functioning (P≤0.01), role-emotional functioning (P≤0.01), and vitality (P≤0.01). In addition, the scale scores of physical functioning, general health, and vitality of the patients who were younger than 30 years old at the time of RTx were significantly higher than those of the patients who were older than 30 years, while the scores of bodily pain, general health, and physical functioning were significantly lower in cadaveric graft recipients compared with living-related graft recipients. The study demonstrated an improvement in HRQOL in renal transplant patients from before to 1 year after successful RTx. The results have shown that the
recipients' age at RTx and the type of donor were important factors affecting the HRQOL (Balaska, Moustafellos et al. 2006).

Most commonly RTx is limited by the shortage of kidney donation. During the last decade, Greece has been on the lowest places by RTx rates worldwide (USRDS 2011). A study by Kaitelidou et al. (2005) has come to the conclusion that besides facing a problem in donated organ management, there are also social and cultural factors influencing willingness to donate organs in Greece (Kaitelidou, Ziroyanis et al. 2005). In 2006, only 3% of the citizens carried an organ donation card (Eurobarometer 2007). Symvoulakis et al. (2010) has performed a study on 224 Greek primary care users’ willingness to organ donation in two rural primary care settings in the island of Crete. Over 61% of the respondents had concerns that organs might be used for different purposes like medical research. A sizeable minority of respondents (25.6%) were worried that registering as donors is like tempting death, despite the fact that about 95% of the participants did not find organ donation unacceptable because of religious issues. Finally, there was a large gap between the proportion of people actually registered as donors (2.2% of respondents) and those who stated that they were willing to register as kidney donors (45.7%). The main conclusions of this study were that lack of knowledge and information regarding organ donation are the main reasons to negative attitudes related to registration as donors (Symvoulakis, Komninos et al. 2009; Symvoulakis, Stavroulaki et al. 2010).

Table 3.1 ESRD patients’ willingness to participate in a potential program of nocturnal home HD in Greece. 146 patients from 10 HD centers participated in the survey.

Source: (Stavrianou 2007)

<table>
<thead>
<tr>
<th>Willingness</th>
<th>All</th>
<th>Age 0-35</th>
<th>Age 35-60</th>
<th>Age above 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>23</td>
<td>1</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Slightly</td>
<td>23</td>
<td>3</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Moderately</td>
<td>23</td>
<td>1</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Quite a bit</td>
<td>37</td>
<td>7</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Extremely</td>
<td>40</td>
<td>9</td>
<td>18</td>
<td>13</td>
</tr>
</tbody>
</table>

The most cost-effective dialysis treatment for ESRD patients is HHD providing fewer restrictions to everyday life (Thodis and Oreopoulos 2011). At the
moment HHD is not available in Greece. The survey, performed by Stavrianou et al., on participation in a potential program of nocturnal home hemodialysis has shown that 51% of ESRD patients participated in questionnaire expressed willingness to start HHD. More willing were young patients, less than 35 years old (74%), followed by patients between 35 and 60 years old (58%), and less willing were patients older than 60 years old (40%). The results of this survey (Table 3.1) suggest that introducing HHD in Greece could have positive outcomes improving patients’ QOL (Stavrianou 2007).

Another optional type of dialysis that could be introduced in Greece is a satellite HD center. A telemedicine system has been designed and reported by a group of Greek researches. Preliminary clinical trials at four European locations involved 29 patients and 305 sessions of HD. The results indicated that the telemedicine system was capable of satisfying the requirements of formative evaluation as a precursor to evaluating its overall worth (Agroyannis, Fourtounas et al. 1999; Agroyannis, Tzanatos et al. 1999; Skiadas, Agroyiannis et al. 2002). Telemedicine dialysis implementation could undoubtedly be of major importance especially in rural areas of the country. Unfortunately, there is no further literature identifying implementation of the system in Greece.

Study on efficiency measurement of 118 HD units in Greece has been performed by Kontodimopoulos and Niakas (2005). The calculated efficiency scores for the public sector and private sector units were 65.04% and 82.21%, respectively. The units were also classified, according to location, as either being in Athens, Thessalonica or another region. The results yielded mean efficiency scores of 58.89%, 61.48% and 67.51%, respectively. Comparison, in this case, indicated significant differences between the public sector units located in Athens and those located in Thessalonica or elsewhere. These results suggested that diminishing possible inefficiencies within the existing HD units could release resources to be used in a growing need for HD units for treatment of ESRD patients in Greece (Kontodimopoulos and Niakas 2005).
4.1 MARKOV MODELS

Markov models received their name after their creator Andrei Markov (1856-1922), who began to study a new type of chance process in 1907. Markov models are used in many diverse areas, not only in computer science and engineering but also in other disciplines such as mathematics, probability and statistics, operations research, industrial engineering, electrical engineering, biology, genetics and agriculture, economics and demographics, education, and so on (Hillis, Maguire et al. 1986; Jain 1986; Stewart 1994). Markov models have also shown themselves to be a valuable analysis tool in a variety of economic models, from population forecasting to financial planning.

Markov chains and Markov process are two important classes of stochastic processes. Markov process is a continuous time process. On the contrary, the Markov chain is a discrete time process.
The Markov chain is described as follows: a set of states $S_1, S_2, S_i, \ldots S_k$ which makes a space of states $S = [S_1, S_2, S_i, \ldots S_k]$ (Figure 4.1). The process starts in one of those states and moves successively from one state to another (Stewart 1994).

Each move from one state to another is called a step. If the model is currently in state $s_i$, then it moves to state $s_k$ with a probability $p_{ik}$. The probabilities $p_{ik}$ are called transition probabilities (Eq. 4-1). The process can remain in the state it is in, and this occurs with probability $p_{ik}$. An initial probability distribution, defined on $S$ space, specifies the starting state. Usually this is done by specifying a particular state as the starting state.

The fundamental property of a Markovian system, referred to as the Markov property, is that the future evolution of the system depends only on the current state of the system and not on its past history (Norris 1997).

$$TM = \begin{bmatrix} S_1 & S_2 & S_3 & S_k \\ S_1 & p_{11} & p_{12} & p_{13} & p_{1k} \\ S_2 & p_{21} & p_{22} & p_{23} & p_{2k} \\ S_3 & p_{31} & p_{32} & p_{33} & p_{3k} \\ S_i & p_{i1} & p_{i2} & p_{i3} & p_{ik} \end{bmatrix}$$

Eq. 4-1
In Eq. 4-1, the $S_{1...k}$ column components show the state of the system at the time $t$, while the $S_{1...i}$ row components show the state the system will be in at time moment $t+i$. Another Markov model’s property is that the sum of the components in each row equals to 1, since the system can be in only one state at a time.

In Markov chain, the transactions occur at certain time intervals. The time cycle is chosen depending on the system the chain represents. Time can be expressed in any possible time unit. It can be taken to be a second, an hour, a day, a week, a month or a year and so on, depending on the subject.

Depending on the states types Markov chains can be classified into several groups. Three of them are: ergodic chains, regular chains and absorbing chains. A Markov chain is called an *ergodic* chain if it is possible to go from every state to every state (not necessarily in one move). Often, ergodic Markov chains are called irreducible. A Markov chain is called a *regular* chain if some power of the TM has only positive elements. In other words, for some $n$, it is possible to go from any state to any state in exactly $n$ steps. It is clear from this definition that every regular chain is also ergodic. On the other hand, an ergodic chain is not necessarily regular.

One of the types of the Markov model is an absorbing Markov model. A state $s_i$ of a Markov chain is called absorbing if it is impossible to leave it (i.e., $p_{ik} = 1$). A Markov chain is absorbing if it has at least one absorbing state, and if from every state it is possible to go to an absorbing state (not necessarily in one step). Absorbing state is a terminate state (purpose of walk, stop, death etc.)

A *nonregular* Markov chain is a chain having absorbing state(s) equal to zero. In all powers of $P$ in nonregular Markov Chain the chain will contain zero. For example,

Let

$$P = \begin{bmatrix} 1 & 0 \\ 0.5 & 0.5 \end{bmatrix}$$

be the TM of a Markov chain. Then, all powers of $P$ will have 0 in the upper right-hand corner.

$$P^6 = \begin{bmatrix} 1 & 0 \\ 0.94 & 0.06 \end{bmatrix}$$
The initial or a start behavior of the system is often defined separately by the initial probabilities distribution vector. The initial probability vector is a raw vector with non-negative components whose sum equals to one. In order for the system start to evolve, the initial transition probability distribution vector is multiplied by the transition probabilities matrix. This means that having the initial probabilities distribution and TM, we can find out what will be the initial probabilities at the next step (Sendi, Craig et al. 1999).

In the long-range predictions are independent of a starting state. The matrix of n-step transition probabilities is obtained by multiplying the matrix of one-step transition probabilities by itself (n-1) times, in other words:

\[ P^n = P \cdot P^{(n-1)} = P^n \]

Eq. 4-4

A probability vector with r components is a row vector whose entries are non-negative and sum to 1 (the system can be in one state at a time t). If \( \mathbf{u} \) is a probability vector which represents the initial state of a Markov chain, then the i-th component of \( \mathbf{u} \) is representing the probability that the chain starts in state \( s_i \) (Stewart 1994).

Let \( P \) be the TM of a Markov chain, and let \( \mathbf{u} \) be the probability vector which represents the starting distribution. Then the probability that the chain is in state \( s_i \) after \( n \) steps is the i-th entry in the vector

\[ u^n = \mathbf{u} P^n \]

Eq. 4-5

A process that can reach a finite number of states is called discrete-time process (Jensen and Bard 2002). The term Markov chain is used to mean a Markov process which has a discrete (finite or countable) state-space. A continuous or infinite process is possible, when the transitions out of state depend on the time t. The Markov process is then said to be non-homogeneous (Kempthorne 1971). When transitions are independent of time of the observation (constant regardless of time), the Markov process is said to be homogeneous (Beck and Pauker 1983).

4.2 MARKOV MODELS IN MEDICAL DECISION MAKING

Of several mathematical models that occur to serve as adjunct to the clinical decision making process, the Markov model is distinguished by its simplicity, its ease of use and its accurate representation of many clinical problems.
In a patient prognosis model it is assumed that the patient is in one of the finite number of states of health. A simple example of such a model consisting of three medical states: Well, Ill and Dead is illustrated in Figure 4.2.

The length of the cycle in medical models is chosen to represent a clinically meaningful time interval. For a model that spans the entire life history of a patient and relatively rare events the cycle length can be one year. Often the choice of a cycle time is determined by the available probability data.

The Markov process is completely defined by the probability distribution among the starting states and the probabilities for the individual allowed transitions.

In medical problems, the matrix presented in the previous subchapter (Eq. 4-1) would be translated as follows. The rows represent the current health state and the columns represent the future state. The sum of the row probabilities equals to one since each health state is independent of the other. The diagonals represent the probability of staying in the same health state. In medical problems, the “dead” state is an absorbing state: the probability to leave the state equals to zero and the probability to stay in the state equals to one.

During a Markov model creation for medical decision making it is important that all clinical states are clearly defined. Importantly, they should enable estimation of the specific transition probabilities per unit time among these states.

There are two types of states considered in Markov medical decision making models: temporary and long-term states. Temporary states reflect short-term events...
that force transition to another state in the next cycle. Long term states are states in which it is possible to remain from cycle to cycle.

In the clinical literature, state transitions are commonly expressed as rates. Rates can range from zero to infinity and are expressed per unit time. Probabilities on the other hand vary from one to zero and have time built in them implicitly.

The rate of transition \( R(t) \) equals to the number of patients that have changed treatment therapy from \( S_1 \) to \( S_2 \) divided by the number of patients on therapy \( S_1 \) at a given time \( t \):

\[
R(t) = \frac{tS_1S_2}{tS_1} \quad \text{Eq. 4-6}
\]

For any rate \( r \), the probability of an event occurring over a time interval of \( t \) time units is calculated by the following formula:

\[
P[t] = 1 - e^{-rt} \quad \text{Eq. 4-7}
\]

where \( P[t] \) is the probability of moving to state \( S \) at time interval \( t \) and \( r \) is the rate of transition.

The expected time before absorption can be calculated in three ways: a Monte Carlo simulation of a large series of individual patients, a probabilistic simulation of a cohort of patients, and, for a Markov chain only, a matrix algebra solution (Beck and Pauker 1983).

In medical Markov models, the time until the process is absorbed is a patient’s life expectancy. The life expectancy is defined as the average future lifetime of a cohort of patients with identical clinical features. The enumeration of states and the assignment of transition probabilities are sufficient to calculate life expectancy with the Markov model. Monte Carlo techniques in medical decision making are discussed further on in this thesis.

4.3 MARKOV MODEL VALIDITY

Sensitivity analysis and data splitting techniques can be used to critique the model. These methods reveal inconsistencies in the model, rather than specifically test the assumptions. Inconsistencies may reflect violation of assumptions or other problems such as imprecise estimates or flawed data.
Data splitting is separating the data set and using one portion to fit the model. The model is used to predict the expected state distribution for a future time period that is compared to the observed state distribution of the remaining data already collected (Lawless and Yan 1993; Schaubel, Morrison et al. 1998). If the data is dense enough, separate models may be fitted for several different time intervals and compared, giving a method of internal validation of the model (Schaubel, Morrison et al. 1998; Sendi, Craig et al. 1999).

Sensitivity analysis provides a tool for studying the behavior of the model (Sendi, Craig et al. 1999; Aoki, Kajiyama et al. 2000). It does not provide any confidence statements about the results. One-way sensitivity analysis provides an incomplete estimation of uncertainty because the results are a function of the entire matrix and not just a single probability. Sensitivity analysis puts the probability of variables in the model through a range of possible values (0 to 1) and the outcome of the model is examined. Traditional one-way sensitivity analysis examines one variable at a time (Aoki, Kajiyama et al. 2000). Manipulation of two or more variables together becomes complex because a two or more dimensional polyhedron rather than a single line describes the range of values (Jensen and Bard 2002).

The model’s predictive validity can be tested by comparison of predicted final or intermediate outcomes with observed outcomes of a separate cohort (Sendi, Craig et al. 1999). An independent data source suitable for comparison may be difficult to find and data splitting can be used as an alternative measure (Lawless and Yan 1993; Schaubel, Morrison et al. 1998; Sendi, Craig et al. 1999).

4.4 MONTE CARLO TECHNIQUES IN MARKOV CHAIN MODEL FOR MEDICAL DECISION MAKING

Monte Carlo Markov Chain is a general purpose technique for generating fair samples from a probability in high-dimensional space, using random numbers (dice) drawn from uniform probability in certain range. A Markov chain is designed to have \( \pi(x) \) being its stationary (or invariant) probability (Figure 4.3).
Monte Carlo simulation random number generator is used to assign a value to each of the random variables (states) in accordance with its probability distribution (transition probabilities).

Monte Carlo disease simulation is a modelling technique that operates on a patient level basis, explicitly estimating the effect of variability among patients in both underlying disease progression patterns and in individual responsiveness to treatments. Typical outputs from these simulations are patient functional status, life years, quality-adjusted life years, and associated costs, all of which can be appropriately discounted.

Monte Carlo disease simulation also allows decision makers to address the question of risk associated with smaller populations that may not tend to the "average" results generated by Markov models or simulations of large populations.

In individual Monte Carlo Simulation patients traverse a Markov process one by one, with a random number generator determining what happens to the individual at each cycle of the process. Each patient begins in the initial state or in one of a limited distribution of states of health (e.g. WELL in Figure 4.4). At each cycle the patient changes state according to the laws of chance, as dictated by the transition probabilities. A clock cycle length is defined, and a cycle counter increments with each transition. When the patient enters the absorbing DEAD state, the current cycle count represents the length of his or her individual life (Figure 4.4). While a patient is traversing the temporary states of the model, the length of time in each non absorbing state is recorded.
Research, design and development of software tools for process management in the area of e-health

Figure 4.4 A MCMC simulation. The lines represent the trajectory of an individual patient through the Markov chain model. This patient is in WELL for three cycles, becomes ILL in the fourth cycle, and dies in the sixth cycle. Source: (Beck and Pauker 1983)

After the first person has completed the simulation (i.e. has died), another patient begins in one of the initial states and a new simulation is performed. After a large number (on the order of $10^4$) of identical patients have been simulated, with each individual trajectory through the Markov process governed by the laws of chance, the averaged number of cycles before absorption (death) is equivalent to life expectancy. Similarly, the averaged or expected number of cycles in each nonabsorbing state may be calculated. Of course, since it is known for each simulated patient not only how long he spent in each nonabsorbing state but also when these nonabsorbing cycles occur, the effect of changes in the utility of each state over time could be simulated (e.g. discounting of decreasing marginal value).

A Monte Carlo simulation is equivalent to the performance of a large number of experiments with the Markov chain model. Its accuracy is as good as the number of patients simulated, the quality of the random number generator used, and our knowledge about the initial state and transition probability distribution. Because each patient must be simulated individually, the approach is time-consuming. On the other hand, because the process is a simulation, the probabilities and utilities can easily change as function of time. Thus, Markov chain models with time-dependent probabilities may be studied with the Monte Carlo approach. Since patients are simulated as individuals this approach provides the greatest flexibility and detail. In particular, measures of variability around life expectancies are easy to calculate.
Monte Carlo simulation is time consuming but allows considerable flexibility. Subjects can start in different health states, varying utilities can be applied and time-dependent probabilities can be incorporated. The variance of estimates is close-formed and easy to calculate. Increasing the number of simulations will reduce the variance of the estimates (Beck and Pauker 1983; Briggs and Sculpher 1998; Meerschaert 1999).
Chapter 5

ESTIMATING MARKOV CHAIN TRANSITION MATRICES USING PROPORTIONS DATA ON ESRD IN GREECE

5.1 DATA ON ESRD PATIENTS IN GREECE

The data on patients’ prevalence and incidence used in the current thesis were obtained from ERA-EDTA annual reports for the years 1998-2009 (ERA-EDTA). The annual data on ESRD patients in Greece are provided to the ERA-EDTA Registry by the Hellenic Renal Registry. The Hellenic Renal Registry, supported by the Hellenic Society of Nephrology, started functioning as a national registry in 2000, under the Board of Registry Coordination and Control of RRT and RTx (in Greek: Υπηρεσία Συντονισμού και Ελέγχου Εξωνεφρικής Κάθαρσης και Μεταμορφώσεων (ΥΣΕ)), a state body attached to the Ministry of Health, which keeps the records of ESRD patients from 1986.

The incident patients’ number refers to all patients that started RRT for ESRD during the year studied in the report. The prevalent patients’ number refers to all
patients who were alive and on RRT or living with functioning renal graft on December 31st of the year examined in the report.

The number of incident patients used in the present work is the number of patients on the 91st day of the treatment. The initial mode of dialysis is determined at 90 days after first treatment, to exclude patients with established renal failure who die and those having acute renal failure requiring HD and having recovered renal function, thus not needing chronic therapy (Chambers, Brown et al. 2010).

For the purpose of this work, in order to gain simplicity and accordance with available transition matrices in literature, the prevalent and incident counts available in ERA-EDTA reports for five age groups (0-19, 20-44, 45-64, 65-74 and 75+) were regrouped into three age groups: <45, 45-65 and >65 years old. Data from several types of tables from reports were combined in order to estimate the data applicable for the projection model presented in this thesis. In order to estimate the number of patients by therapy in each age-specific group the total number of patients was multiplied by percentages of established therapy. All the data used in the projection model are presented in Appendix B. Estimated age-specific incident patients’ number by therapy is presented in Table B.1 in Appendix B. Data on total incidence by age group, established therapy and in total are presented in Appendix B, Table B.2.

Data on prevalent patients’ statistics are summarized in Table B.3 that reveals the age-specific patients’ number by therapy and in table B.5, presenting the total counts by therapy, age group and in total. These tables may be found in Appendix B.

During model implementation, no distinction was made between the primary and sub-primary types of therapy; thus HD includes patients on HD, hemodiafiltration and hemofiltration. PD includes patients undergoing APD and CAPD. RTx includes patients independently on different donor types, living and deceased.

5.2 PROJECTION MODEL USING MARKOV CHAIN

The number of prevalent patients $P$ distributed by therapy for the next year $(t+1)$ was calculated using the number of prevalent patients distributed by therapy from the previous year $t$ as shown in Eq. 5-1:

$$ P(t+1) = P(t) * TM + I(t+1) * I_d $$

Eq. 5-1
where TM is the transition matrix, \( I \) is the number of the incident ESRD patients that have started therapy within the year \((t+1)\) and \( I_d \) is a vector that contains patients’ initial assignment probabilities to the HD, PD or RTx.

![Markov Chain model diagram](image)

*Figure 5.1 The possible transitions of the prevalent patients between the states of the Markov Chain model*

The prevalent patients’ behavior is described by the transition matrix that consists of three mutually exclusive treatment states: HD, PD and RTx and one absorbing state, Death (Figure 5.1). The possible transitions between the states are shown by the arrows. The backward bending arrows show the possibility for the patients to remain in the state they were in during the previous cycle.

![Incidence by age group](image)

*Figure 5.2 Incident patients number, \( I \), by age group for the period 1998-2009.*

The number of the incident patients with ESRD in Greece, \( I \), is depicted in Figure 5.2 for three age groups for the period 1998-2009. ESRD incident patients’
number by age group, therapy and in total in Greece is presented in Table B.1, Appendix B.

The $I_d$ vector has the form of $[I_{HD} I_{PD} I_{RTx} I_{Death}]$ representing the possibility of a patient to be assigned to one of the three therapies, while $I_{Death}$ was set to zero in order to perform matrix multiplication. The overall probability of $I_d$ equals to 1. The incident patients' distribution probabilities by age group and therapy for the period 1998-2008 are presented in Table B.6, Appendix B.

For the first year of the simulation, 1998, the P(t) was calculated by multiplying the total number of prevalent patients by the therapy assignment vector concerning that year. This vector in the form of $[P_{HD} P_{PD} P_{RTx} P_{Death}]$ represents the possibility $P$ of a patient to be assigned to one of the three therapies, while $P_{Death}$ is set to zero.

### 5.3 TRANSITION MATRIX OF THE MARKOV CHAIN

The TM is a four by four matrix holding transition probabilities. Each probability represents the estimated likelihood of changing from one state to another during a finite time interval. The TMs was calculated based on a priori knowledge and aggregate data from previous years by using a least squares estimator technique. In circumstances where individual transitions are not observed proportions data are used to estimate Markov chain TMs (Lee, Judge et al. 1970; Kalbfleisch and Lawless 1984). The model employs three different TMs, one for each specific age group (<45, 45-65, >65) generally noted as:

$$\begin{bmatrix}
I_{HD} & I_{PD} & I_{RTx} & I_{Death} \\
\begin{bmatrix}
a_{11} & a_{12} & a_{13} & a_{14} \\
a_{21} & a_{22} & a_{23} & a_{24} \\
a_{31} & a_{32} & a_{33} & a_{34} \\
a_{41} & a_{42} & a_{43} & a_{44} \\
0 & 0 & 0 & 1
\end{bmatrix}
\end{bmatrix}$$

where $i$ is 1,2,3,4 and all $a \geq 0$ (e.g. $a_{12}$ is the likelihood of a patient on HD therapy to change for PD therapy).

By definition, the transition probabilities of the Markov chain model are non-negative values and their sum by rows equals to one as shown in Eq. 5-3.

$$a_{11} + a_{12} + a_{13} + a_{14} = 1$$
In the absence of observed individual transitions of the patients between the therapies or large prospective observational studies conducted in Greece, this study uses the best available national and international published data to calculate the TMs. The TMs were calculated based on the available data from several publications, by grouping the data into upper and lower limits of possible transitions between the states (Vestergaard and Lokkegaard 1997; Schaubel, Morrison et al. 2000; Kirby and Vale 2001; FRKD 2001-2008; Ioannidis, Papadaki et al. 2002; Teerawattananon, Mugford et al. 2007). The data in net transitions were transformed into probabilities by Eq. 4-7 proposed by Beck and Pauker (Beck and Pauker 1983). The available TMs in the literature did not always concern the specific age groups defined for ESRD population in Greece. The transition probabilities obtained from the literature regarding the total number of RRT patients, were also taken into account in defining the upper and lower bounds of each age-specific group. For further details on obtained transition probabilities from the literature please refer to Appendix C.

The transition probabilities values for ESRD patients are kept in a certain proportion, i.e. the majority of patients stay at the same treatment, while the minority change the main treatment, e.g. from HD to RTx, from RTx to PD or HD, or from PD to RTx. Thus, providing proportions of the transition probabilities from other countries is applicable for Greece in case the range of each transition probability is wide enough to search for the optimal solution.

For each transition probability, we constructed the confidence interval. The upper and lower bounds of a 67% (±1σ) confidence interval for each transition probability were assigned as upper and lower limits in order for the least square estimator to search for an optimal solution.

The least squares estimator was applied separately for each age group to obtain the corresponding TMs. Data splitting technique was used for implementing the TMs of the Markov chain model and testing their adequacy (Lawless and Yan 1993; Schaubel, Morrison et al. 1998). The data splitting technique separates the available data in two groups, the training and the validation data. In this study, the data for the period 1998-2006 were used as training data, while those of the period 2007-2009 were validation data. During the validation process, the incidence projection model was used. In this way the incidence model was also tested for its adequacy.

The training phase includes the following. The initial TM was filled up with the mean values calculated from the upper and lower bounds for each transition probability. In each iteration of the least squares estimator, the number of patients
distributed by therapy $P(t+1)$ was calculated, according to Eq. 5-1 for every year of the training period. The mean error between the estimated and the real prevalent patient numbers was calculated. Then, each transition probability was modified by a small fraction of the difference (upper minus lower bound) in both directions. Each transition probability was updated in the direction that resulted in a decrement of the mean error. This iterative process in finding the values of the TM converged at a minimum error below 5%. The obtained upper and lower bounds are presented in Table 5.1.

Table 5.1 Estimated upper and lower limits for the three age groups, <45, 45-65 and >65 years old, based on literature review

<table>
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<th>&lt;45</th>
<th>45-65</th>
<th>&gt;65</th>
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<tbody>
<tr>
<td></td>
<td>0.477-1.000</td>
<td>0.000-0.220</td>
<td>0.000-0.160</td>
</tr>
<tr>
<td></td>
<td>0.000-0.417</td>
<td>0.233-0.937</td>
<td>0.000-0.316</td>
</tr>
<tr>
<td></td>
<td>0.000-0.052</td>
<td>0.000-0.050</td>
<td>0.738-0.989</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The model did not take into account transitions between the age groups, thus mortality rates for age groups >45 and 45-65, actually include death probability and probability to change age group.

The validation process included calculation of the number of patients distributed by therapy $P(t+1)$ (Eq. 5-1) for the period 2007-2009 using the estimated TMs and the incidence projection model. The absolute errors for the validation data are presented separately in the next chapters.
6.1 INCIDENCE PROJECTIONS

Three basic Incident Rate (IR) scenarios were modeled, based on data for the total incidence of ESRD in Greece (ERA-EDTA). In the first IR scenario, called low IR scenario, the IR was maintained at the level it was in 2009. In the second IR, the medium one, a logarithmic trend was assumed, maintained over the period of prediction, while the third IR (high) scenario presents a linear trend over the period to 2020.

The total number of incident patients in pmp was projected using the three IR scenarios. Patient numbers in pmp was turned into counts using the general population number prediction for Greece, in order to be used in the model. Data on population projections from 2007 to 2050, based on estimated population on January 1st 2007, were available in the Hellenic Statistical Authority (EL.STAT), calculated
in three time series: low, high and medium. The medium time series was exploited for the conversion of the incident patients in pmp to counts \((EL.STAT)\).

![Figure 6.1 Three scenarios of incidence prediction to 2020: low IR, medium IR and high IR. 1998-2009: real data, 2010-2020: projection.](image)

In order to calculate the number of incident patients per age group \(I_{<45, 45-65, >65}\) (see Eq. 5-1), the total incident patients’ number was multiplied by the average percentage of the patients taken for the period 2005-2009 within each age group. The distribution by therapy (vector \(I_d\) in Eq. 5-1) for the projection model was taken as an average vector based on data available for the years 2005-2009. For age-specific average distributions of incident patients in Greece please refer to Table B.6 in Appendix B.

During the period 1998-2009 the incident patients’ number on PD in age group > 65 varied between 65 and 129 patients with no trend detected. For this specific case, the number of incidence patients on PD was projected by taking the average patients’ number being on PD treatment during the period 1998-2009.

### 6.2 PREVALENCE PROJECTIONS

The projection of the future patients’ number with ESRD in Greece was calculated by Eq. 5-1 presented in the subchapter 5.2 of the current thesis. For the
initial year of the simulation, 2009, the distributions of the prevalent patients by therapy available from the ERA-EDTA reports were used.

### 6.3 INCREASE OF THE TRANSPLANTATION RATES

Two scenarios of increased transplant supply were simulated in order to investigate the impact on RTx prevalence. The first scenario (scenario 1) assumed that the average number of transplantations performed in Greece during the period 2005-2009 will double by 2020. Starting from 2010, the number of transplants will increase from 20.8 pmp to 41.6 pmp in 2020. The second scenario (scenario 2) assumed that Greece will reach by 2020 the transplantation rate of Norway in 2009, which corresponds to 60.5 pmp. According to the USRDS report concerning the year 2009, Norway had the highest rate of prevalence in functioning grafts worldwide and the highest transplantation rate in Europe (USRDS 2011).

![Graph showing two scenarios of increase in RTx rates, scenario 1 – double increase of transplantations performed in Greece during the period 2005-2009 on average. Starting from 20.8 pmp in 2010 and resulting in 41.6 pmp by 2020. Scenario 2 – Norway practice of 60.5 transplantations pmp in 2008, achieved in Greece by 2020.](image)

Thus two objectives of 41.6 and 60.5 pmp transplants by 2020 were set. This type of increase was mathematically described by tanh(x) function for both scenarios,
depicted in Figure 6.2. For model simplicity no distinction was made between living and cadaveric transplant.

It was assumed that if a campaign targeting increase in RTx would start in Greece in 2010, then during the first years it would have minor effect on the number of performed transplantations, but would then be followed by a more rapid increase, finally stabilizing at its peak.

To reflect the new numbers of transplants performed every year, the transition probabilities that concern the possibility of a patient to move from HD to RTx and to remain on HD therapy were modified properly. The number of prevalent patients’ was projected based on (Eq. 5-1) the medium IR scenario.

6.4 MODEL SENSITIVITY ANALYSIS

Model sensitivity analysis was performed in order to evaluate the uncertainties of the current projection model output, attributed to different variations of the calculated TMs. In order to perform the sensitivity analysis, each transition probability was broadened by 10%. Then the projection was performed 1000 times, each time drawing different TMs within the bounds, while at the same time keeping the overall probability equal to 1. Monte Carlo techniques were used to sample the probability distributions given in the TM and to simulate treatment change for the prevalent and incident patients. The sampling was accomplished from the cumulative distribution functions calculated from the transition probabilities in each row of the TMs. Monte Carlo approach was also explored to estimate the initial assignment of incident patients to ESRD therapies. Sensitivity analysis was performed based on the projection with medium IR scenario.

6.5 COST-EFFECTIVENESS ANALYSIS

The annual cost per patient associated with the treatment modality (HD, PD or RTx) calculated by Kontodimopoulos and Niakas et al. (2008) for 2003 was used to perform cost-effectiveness analysis of the scenario and base-case prediction (Kontodimopoulos and Niakas 2008). The average cost in Euros per HD and PD therapy was equal to €36,247 and €30,719 respectively. The cost of RTx from a living donor for the first year of the treatment was €33,318, for the second year €5,379 and
for the years after €5,238. For diseased donor RTx, the first year cost was €30,109, the second year cost was €6,654, while the annual cost for the following years was €5,851. During the period 2002-2009 average relation of the grafts received from living donor versus deceased donor was about 38.5:61.5%, which was used while performing RTx costs calculations (ERA-EDTA). The data on performed RTx in Greece during the period 2002-2009 are presented in Table B.4 in Appendix B.

6.6 RESULTS

6.6.1 Transition matrices

The TMs were estimated based on the proportional data available for Greece using a least squared estimator. The least squares estimator applied to data 1998-2006 resulted in the following age specific TMs:

\[
TM_{<45} = \begin{bmatrix}
0.750 & 0.033 & 0.065 & 0.152 \\
0.273 & 0.409 & 0.139 & 0.179 \\
0.023 & 0.004 & 0.945 & 0.028 \\
0 & 0 & 0 & 1
\end{bmatrix}
\]

\[
TM_{45-65} = \begin{bmatrix}
0.780 & 0.041 & 0.025 & 0.154 \\
0.299 & 0.405 & 0.120 & 0.176 \\
0.025 & 0.007 & 0.946 & 0.022 \\
0 & 0 & 0 & 1
\end{bmatrix}
\]

\[
TM_{>65} = \begin{bmatrix}
0.805 & 0.001 & 0.013 & 0.181 \\
0.178 & 0.745 & 0.004 & 0.073 \\
0.061 & 0.001 & 0.756 & 0.182 \\
0 & 0 & 0 & 1
\end{bmatrix}
\]

Eq. 6-1

The model was implemented in MATLAB.

6.6.2 Validation

The Markov chain model was validated on data for the period from 2007 to 2009. The medium IR scenario was used as a base for the validation. Validation process included comparison of the estimated total number of prevalent patients by age group and therapy to real data.
Table 6.1 Validation error expressed in per cent difference, estimated by comparison of real and simulated data.

<table>
<thead>
<tr>
<th>Year</th>
<th>HD</th>
<th>PD</th>
<th>RTx</th>
<th>&lt;45</th>
<th>45-65</th>
<th>&gt;65</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>1.50</td>
<td>2.71</td>
<td>2.28</td>
<td>1.10</td>
<td>2.61</td>
<td>4.18</td>
<td>0.83</td>
</tr>
<tr>
<td>2008</td>
<td>3.21</td>
<td>2.64</td>
<td>5.02</td>
<td>0.43</td>
<td>3.72</td>
<td>5.52</td>
<td>1.47</td>
</tr>
<tr>
<td>2009</td>
<td>2.11</td>
<td>3.89</td>
<td>3.94</td>
<td>0.70</td>
<td>4.22</td>
<td>4.68</td>
<td>1.00</td>
</tr>
</tbody>
</table>

The results of the validation are presented in Table 6.1. It contains the error (absolute value) in percentage between real and modeled number of patients on the different treatment modalities (HD, PD and RTx), the three age groups and total number of patients with ESRD (in the last column).

Absolute validation error varied from 0.43% to 5.52%. The latest and highest validation error is in the age group >65 years old. Validation error for the total number of ESRD patients varied from 0.83% to 1.47%.

6.6.3 Prevalence projections

The results of the predicted number of ESRD patients are presented in Table 6.2. A substantial increase of ESRD prevalence is predicted for all three IR scenarios. Even in the case of the low IR scenario, which maintains the IR on the level of 2009 during the projection period, an annual increase of about 1.6% in total prevalence is observed. Regarding the other two IR scenarios the total prevalence increase was even higher. The medium IR scenario projected a 2.01% per annum (p.a) increase, while the high IR scenario predicted a 3.26% p.a. increase in prevalent patients’ number.

The total number of patients in 2020 is anticipated to reach 14332, 14953 and 17095 for the low, medium and high IR scenarios, respectively.
Table 6.2 Results of three IR scenario types. Increase per annum (p.a.) and overall increase (↑) during the period 2009-2020 are calculated in percentages. N is the number of patients.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>&lt;45</th>
<th>45-65</th>
<th>&gt;65</th>
<th>Total</th>
<th>HD</th>
<th>PD</th>
<th>RTx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low IR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p.a.</td>
<td>1.13</td>
<td>1.12</td>
<td>2.09</td>
<td>1.62</td>
<td>1.54</td>
<td>0.89</td>
<td>2.08</td>
</tr>
<tr>
<td>N of patients in 2020</td>
<td>2095</td>
<td>4687</td>
<td>7550</td>
<td>14332</td>
<td>10446</td>
<td>839</td>
<td>3047</td>
</tr>
<tr>
<td><strong>Medium IR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p.a.</td>
<td>1.21</td>
<td>1.43</td>
<td>2.62</td>
<td>2.01</td>
<td>2.04</td>
<td>1.09</td>
<td>2.16</td>
</tr>
<tr>
<td>N of patients in 2020</td>
<td>2112</td>
<td>4851</td>
<td>7992</td>
<td>14953</td>
<td>11024</td>
<td>857</td>
<td>3073</td>
</tr>
<tr>
<td><strong>High IR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p.a.</td>
<td>2.39</td>
<td>2.59</td>
<td>3.93</td>
<td>3.26</td>
<td>3.50</td>
<td>1.95</td>
<td>2.74</td>
</tr>
<tr>
<td>↑ (2009 - 2020)</td>
<td>29.66</td>
<td>32.52</td>
<td>52.82</td>
<td>42.24</td>
<td>45.96</td>
<td>23.65</td>
<td>34.62</td>
</tr>
<tr>
<td>N of patients in 2020</td>
<td>2400</td>
<td>5497</td>
<td>9198</td>
<td>17095</td>
<td>12885</td>
<td>941</td>
<td>3270</td>
</tr>
</tbody>
</table>

The highest annual increase was observed in patients older than 65 years old. This average increase corresponds to 2.09%, 2.62% and 3.93% per annum for the three IR scenarios, respectively (Table 6.2). The total percent increase of ESRD patients in 2020 compared to 2009 in this age group is predicted to be 25%, 33% and 53% for the low, medium and high IR scenarios respectively.
The lowest annual increase (1%) was projected for PD amongst the three treatment modalities. The annual prevalence increase for HD and RTx was about 2%. All three IR scenarios had the highest impact on HD projections resulting in sufficient difference in the predicted number of patients in 2020 (Figure 6.3). The expected HD prevalent patients’ number in case the high IR scenario is applied resulted in almost 2500 patients more than in case of low IR scenario.

### 6.6.4 Transplant supply scenario

The two scenarios of higher transplant supply were simulated and the projected ESRD prevalent patients’ number in 2020 by therapy was compared to the results obtained with the medium IR scenario.

The projection when medium IR is applied resulted in 26.5% (see Table 6.2) increase in RTx prevalence that corresponds to 644 more patients by 2020 compared to 2009. Increasing the transplant supply based on scenario 1 and 2 results in RTx prevalence increase from 2009 to 2020 by 64.6% (1570 more patients) and 107.2% (1950 more patients) respectively.

Both scenarios had a substantial impact on the proportion of the ESRD patients on HD and RTx. In 2020, the percentage of the prevalent patients on RTx...
increased from 20.2% (medium IR scenario) to 26.3% in case of scenario 1; expressed in numbers, this increase of 6.1% corresponds to 926 patients. Similarly, an increase of 12.4% corresponding to 1959 RTx prevalent patients was projected with scenario 2 compared to medium IR scenario in 2020. At the same time, the projected percentage of the patients on HD is expected to decrease from 73.7% in case of medium IR by 5.6% and 11.6% for scenario 1 and 2, respectively, in 2020. The projected ESRD prevalent patients’ numbers in 2020 by therapy in proportions based on the scenarios 1 and 2 versus projection based on medium IR scenario is depicted in Figure 6.4.

![Figure 6.4 Projected ESRD prevalent patients’ numbers in 2020 by therapy in proportions based on the transplant supply scenarios versus projection based on medium IR scenario.](image)

Higher transplant supply has no considerable impact neither on the patients’ distribution by age group or on the total number of patients.

### 6.6.5 Model sensitivity analysis

The results of the model sensitivity analysis are presented in Figure 6.5 by age group and in Figure 6.6 by therapy.
Figure 6.5 The results of model uncertainty analysis. Prevalence projection by age group, solid lines indicate mean values and dashed lines indicate minimum and maximum values respectively.

Figure 6.6 The results of model uncertainty analysis. Prevalence prediction by therapy, solid lines indicate mean values and dashed lines indicate minimum and maximum values respectively.

In both figures the solid line presents the mean projection value and the dashed lines the minimum and maximum projection values.
6.6.6 Cost-effectiveness analysis

The total expenses for the treatment of the future ESRD patients in Greece during the period 2010-2020 were calculated to reach €4.37 billion for the base-case projection while €4.32 billion for scenario 1 and €4.25 billion for scenario 2. An annual cost of €429.5 million of the ESRD patients’ treatment was calculated for the base-case prediction compared to €415.7 million for scenario 1 and €399.2 million for scenario 2 in 2020. Performing more RTx would result in total saving of €50.2 million in case of scenario 1 and €112.4 million in case of scenario 2 during the period 2010-2020.

6.7 DISCUSSION

A projection model using Markov chain was developed and validated for the prediction of the future ESRD patients’ number in Greece for the period 2010-2020 based on available patients’ statistics covering twelve years (from 1998 to 2009). The model was successfully verified by reproducing the number of patients by therapy, age group and in total for the period 2007-2009, based on data for the period 1998-2006. The comparison of actual and estimated number of prevalent patients by age group, therapy and in total for the period 2007-2009 showed discrepancies in the range from 0.43% to 5.52%.

The total projected ESRD prevalence, estimated with the low, medium and high IR scenario, is expected to reach 1233.6, 1287.0 and 1471.4 patients pmp, respectively. The high IR scenario resulted in 42% prevalence increase during the period 2010-2020. Specifically, there were 12018 ESRD patients in 2009 and according to the Markov chain model the number of patients on therapy will reach 17095 in 2020.

Continuous increase in prevalence by 2020 is predicted for all three scenarios applied. Even with the low IR scenario an annual increase of 1.62% in the total prevalence is predicted. The highest impact was observed in the RTx therapy group and in the group of patients >65 with a 2.1% p.a. increase.

The model used least squared estimator for generation of TMs for the ESRD population dynamics in Greece, based on data available in national and international publications. The comparison of actual and estimated number of prevalent patients by
age group, therapy and in total for the period 2007-2009 showed discrepancies from 0.4% to 5.5%. The highest error, 5.5%, was on the estimated number of prevalent patients of age 65 and older. It is worth mentioning that, during the validation period no trend was observed in this age group. The sensitivity analysis of the model showed that even with a maximum 10% variation in each transition probability, the results continue to show reasonable consistency.

The simulation of three incidence scenarios indicated prevalence dependence on the incidence rates. Similar conclusion was reported by other studies published in the literature (Vestergaard and Lokkegaard 1997; Branley, McNeil et al. 2000; Roderick, Davies et al. 2004). The continuous increase in prevalence projected by the current model, especially for the age group >65 years old, is consistent with the studies on ESRD prevalence projections for Denmark, Norway, Australia, the U.S. and England (Vestergaard and Lokkegaard 1997; de Wit, Ramsteijn et al. 1998; Schaubel, Morrison et al. 1998; Branley, McNeil et al. 2000; Xue, Ma et al. 2001; Roderick, Davies et al. 2004; Gilbertson, Liu et al. 2005).

The incidence of ESRD in Europe and Greece seems to be stabilized over the last several years. However, analysis of Greek data from 1998 to 2009 shows that for some years there is a trend towards increased incidence that is then stabilized again. Stabilization in incidence is explained by the delay in the progression to ESRD and initiation of the therapy as well as by higher mortality rate of patients in earlier stages of CKD (Kramer, Stel et al. 2009; Zoccali, Kramer et al. 2009). Although a linear trend is unlikely to happen during the next decade, it was used as a possible IR trend to estimate a worst case scenario projection.

As discussed above, the total expected number of ESRD patients in Greece in 2020 is 17095. This number represents an increase of more than 42% in comparison to 2009 (if the worst IR scenario is used in the model). This would result in considerable human, technical and financial resources. Alternatively, other treatment modalities such as HHD and increase in RTx should be considered. At present, HHD which is reported to be more cost-effective compared to CHD and PD (Winkelmayer, Weinstein et al. 2002; Just, Riella et al. 2008), is not well introduced in Greece. The comparison of the studied two RTx scenarios showed that higher transplant supply influenced the proportion of the patients on RTx and HD therapy, while at the same time there was no significant impact on patients’ number by age group and in total. This finding is also in agreement with the results published by Roderick et al. (2004)
(Roderick, Davies et al. 2004). Specifically, the results from the second scenario that considered increase in transplant supply to the level of Norway practice in 2009 showed an increase of 107% in patients on RTx compared to 2009. In numbers this means that the number of prevalent patients on RTx will increase from 2429 in 2009 to 5032 in 2020. At the same time, the total number of ESRD patients on HD would decrease by almost 8.5% in 2020 compared to 2009. Approximately, this would result in total saving of €112.37 million for the period 2010-2020, based on prices available for 2003 (Kontodimopoulos and Niakas 2008). These numbers might be slightly underestimated due to the missing costs of the initial treatment access to the HD and PD treatment alternatives. Normally, the dialysis cost would be higher than estimated.

The simulated increase of RTx during the period 2010-2020 was mathematically described by a tanh(x) function for the two possible scenarios. In order to create a scenario close to reality, it was assumed that if a campaign aiming to promote public awareness about kidney donation together with better kidney graft procurement from cadaver donor would have started in Greece in 2010, it would have minor effect on the number of performed transplantations during the first years, but then this number would rapidly increase and finally stabilize at its peak.

The objective of the first scenario of increase in RTx was to double the average number of performed transplants during the period 2005-2009. The reason for this averaging was sudden and unexpected decrease in number of performed RTx from 265 in 2008 to 168 in 2009. Although there were fluctuations in the annual number of performed RTx over the previous years, in 2009 there was a large decrease below the average. The reason for this change is not known, but it was combined with changes in the personnel of the Hellenic National Transplant Organization (Εθνικός Οργανισµός Μεταµοσχεύσεων).

Almost 75% of ESRD patients in Greece are on HD treatment whereas the number of patients on PD is very small. One of the reasons for this is the presence of a large number of private dialysis units providing HD but not PD. In Greece PD is provided only in central hospitals which have educated staff and facilities for looking after patients on PD. So the small number of patients on PD is explained by the lack of information and patients’ education together with the lack of PD units in non-central hospitals. On the other hand, and despite a more organized attempt of the authorities over the last few years, organ donation is still under the desired level in the country. Low number of transplants in Greece is reported to be due to the significant
gaps concerning both function of the transplant units and the supply organization of
cadaver organs, which remain unsolved (Boletis 2001; Kaitelidou, Ziroyanis et al.
2005). Since 2002, the deceased donor transplant number has been higher than living
donor transplants in Greece, although it has been reported that cadaver donor
transplant has lower survival and is less cost-effective than living donor transplant,
whose cost is continuously decreasing over time (Terasaki, Cecka et al. 1995;
Greek hospital a network of trained professionals responsible for organ procurement
and implementing a living kidney donation promotion program, like those in Spain,
could significantly improve the situation in Greece (Gonzalez Monte, Delgado et al.;
Miranda, Vilardell et al. 2003).
Chapter 7

MARKOV CHAIN MONTE CARLO MODEL FOR ESRD PATIENTS’ PREDICTION IN GREECE

7.1 MARKOV CHAIN MONTE CARLO MODEL

Markov Chain Monte Carlo (MCMC) model comprises a Markov Chain used to predict ESRD prevalent patients’ number in association with Monte Carlo sampling of patient treatment from the estimated transition probabilities.

Monte Carlo techniques were used to sample the probability distributions given in the TMs and to simulate the process of treatment change for the prevalent and incident patients (Rodina-Theocharaki, Bliznakova et al. 2012). The sampling was accomplished from the cumulative distribution functions calculated from the transition probabilities in each row of the TMs. The Monte Carlo algorithm for the simulation the treatment changes and initial treatment assignment of incident patients is depicted in Figure 7.1.
The complete realization of the MCMC model is shown in Figure 7.2. The initial prevalent patients’ population was the ESRD population in Greece distributed by therapy on December 31st 2009. The MCMC model continued with the individual movements’ simulation between therapies for each prevalent patient for the period 2010-2020. Patients who survive a given year repeated the cycle until death or till the year 2020 was reached. The process was repeated for all prevalent patients.
Figure 7.2 MCMC model for estimating the future number of ESRD patients. $P$ is the number of prevalent patients, $P_i$ is a single prevalent patient, $I$ is the number of incident patients, $I_i$ is a single incident patient and $t$ is the year.
New patients that started ESRD treatment were initially assigned to one of the
treatment therapies by utilizing the Monte Carlo algorithm (Figure 7.1). Further on,
these patients are considered to be prevalent, thus the respective algorithm is applied.
The model was implemented in MATLAB. The projected distributions of the number
of patients by therapy and age were obtained from the results of $10^4$ runs of the
MCMC model described in Figure 7.2 using Monte Carlo simulation in order to
achieve less than 1% statistical error.

### 7.2 INCIDENCE PROJECTIONS

The total number of incident patients, ($I$ in Eq. 5-1), for the age group <45 was
modeled by averaged number of patients that were on the treatment during the period
1998-2009. The number of patients in the age group 45-65 was modeled by a linear
regression model based on data available from 1998 to 2009. For the last age group,
>65, the incidence was modeled by logarithmic regression. The projection of
incidence patients is depicted in Figure 7.3.

![Incidence, numbers vs Year](image)

*Figure 7.3 Incident patients prediction for the period 2010-2020.*


The distribution by therapy (vector $I_d$ in Eq. 5-1) for the projection model was
taken as an average vector based on data available for the years 2005-2009. For age-
specific average distributions of incident patients in Greece please refer to Table B.6 in Appendix B.

7.3 PREVALENCE PROJECTIONS

The projection of the future ESRD patients’ number in Greece was calculated by Eq. 5-1 presented in the subchapter 5.2 of the current thesis. The estimation TMs using the least squares estimator is described in Chapter 5.3 of this thesis and the obtained TMs are presented in subsection 6.6.1 (Eq. 6-1). For the initial year of the simulation, 2009, the distributions of the prevalent patients by therapy available from the ERA-EDTA reports were used.

7.4 CASE STUDY: INCREASE OF THE TRANSPLANTATION RATES

The developed MCMC model was used to estimate the impact of an annual increase equal to 1% of the number of incident patients receiving RTx at the expense of HD treatment. The changes started in 2010 and ended in 2020. The subtraction was performed on average $I_d$ vector (Eq. 5-1) based on data for the period 2005-2009 concerning the total number of incident patients. The initial probability assignment of PD patients was left unchanged.

7.5 RESULTS

7.5.1 Validation

The MCMC model was validated on data for the period from 2007 to 2009.

Table 7.1 Validation error expressed in per cent difference (%), estimated by comparison of real and simulated data.

<table>
<thead>
<tr>
<th>Year</th>
<th>HD</th>
<th>PD</th>
<th>RTx</th>
<th>&lt;45</th>
<th>45-65</th>
<th>&gt;65</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>1.9</td>
<td>3.2</td>
<td>2.2</td>
<td>2.4</td>
<td>2.4</td>
<td>5.0</td>
<td>1.2</td>
</tr>
<tr>
<td>2008</td>
<td>4.0</td>
<td>3.9</td>
<td>5.0</td>
<td>1.1</td>
<td>3.4</td>
<td>7.1</td>
<td>2.1</td>
</tr>
<tr>
<td>2009</td>
<td>3.2</td>
<td>6.0</td>
<td>3.9</td>
<td>1.7</td>
<td>3.8</td>
<td>7.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>
During the validation the estimated total number of prevalent patients by age group and by therapy was compared to the real data. The results of the validation are presented in Table 7.1. This table contains the difference between real and modeled number of patients on HD, PD, RTx and by age group. The discrepancy in the total number of ESRD patients is shown in the last column.

Absolute validation error varied from 1.2% to 7.0%. The latest and highest validation error is in the age group >65 years old. Validation error for the total number of ESRD patients varied from 1.2% to 2.0%.

7.5.2 ESRD patients’ projections to year 2020

The annual average increase in prevalence of the ESRD patients for the period 2009-2020 period is expected to be 2.1%, resulting in 15025 patients in 2020 (Figure 7.4).

![Figure 7.4 ESRD patients’ prevalence projection by age group. 1998-2009: real data, 2010-2020: projection.](image)

Specifically, the number of patients that fall in the age group <45 years old will increase by 1.5% in 2020 compared to 2009. Similarly, the number of patients in the group 45-65 will increase by 16.1%. The highest number of patients today of the ESRD population in Greece is in the age group >65 and is predicted to increase by 38.4% in 2020. The total patients’ increase is expected to be 25.0%.
The prediction of patients increase by therapy is depicted in Figure 7.5. The model predicts an average annual 1.4% prevalence increase of patients on RTx from 2009 to 2020. The average annual increase of prevalent HD and PD patients is expected to be 2.1% and 1.7% respectively.

7.5.3 Transplant supply

The scenario of higher transplant supply was simulated and the projected ESRD prevalent patients’ number in 2020 by therapy was compared to the results obtained with the base-case prediction.

The base-case projection resulted in 23.5% increase in RTx prevalence that corresponds to 570 more patients by 2020 compared to 2009. The scenario of increase in transplant supply results in RTx prevalence increase from 2009 to 2020 by 57.9% (1407 more patients).

The scenario had an impact on the proportion of ESRD patients on HD and those on RTx. In 2020, the percentage of the prevalent patients on RTx is predicted to increase from 20.0% to 25.4%; expressed in numbers, this increase of 5.4%
corresponds to 837 patients. The results of the comparison between the scenario and the base-case prediction are depicted in Figure 7.6.

![Figure 7.6 ESRD patients' prevalence projection (base-case) and scenario prediction results by therapy.](image)

With no changes in number of incident patients receiving therapy, the model predicts that there will be 280 RTx performed in 2020. Increasing the number of RTx in new coming patients according to the implemented scenario would result in 524 RTx performed in 2020.

### 7.5.4 Cost-effectiveness analysis

The annual costs per patient associated with the treatment modality (HD, PD or RTx) calculated by Kontodimopoulos and Niakas et al. (2008) for 2003 were used to perform cost-effectiveness analysis of the scenario and base-case prediction and are presented in subchapter 6.5 (Kontodimopoulos and Niakas 2008).

The total expenses for the period 2010-2020 were calculated to be €4.40 billion for the base-case projection and €4.33 billion for the implemented scenario. An annual cost of €433.2 million for ESRD treatments was calculated for the base-case prediction compared to €418.6 million for the scenario in 2020. Performing more RTx
in the same year the new patients start the therapy would result in total saving of €68.2 million during the period 2010-2020.

7.6 DISCUSSION

The MCMC model predicts that in 2020 the number of ESRD patients in Greece will reach 15147, shared in between the age groups as follows: 1970 patients for the <45 age group, 4570 patients for the 45-65 age group and 8607 patients for the >65 age group.

The model used least squared estimator method in order to estimate TMs for ESRD population in Greece, based on TMs for other countries published in national and international publications. The TMs calculation was robust and repeatable while model accuracy was based upon training and validation data. During the model validation phase the highest error was 7.1% on the estimated number of prevalent patients >65 years old. A relatively high error in validation phase was also estimated for PD, 6.0%. The results showed annual increase of 1.7% for the number of PD patients. There are a limited number of centers providing PD in Greece and during the period 2005-2008 the number of patients on this therapy slightly decreased. Unfortunately, this decrease could not be used in the training phase of the model or corrected during the prediction phase like in the Markov chain model resulting in number of PD which might be overestimated. The number of PD patients in age group >65 was averaged in the earlier described Markov chain model, taking into account that no trend was detected. In the MCMC model this technique could not be applied due to the characteristics of the modeling techniques. However, due to the consistency of the training and validation process and the comparable results with other studies for different countries, we believe that the necessity to change therapy assignment policy and the benefits of this in financial terms is clearly demonstrated.

The scenario of increase in RTx simulated by the model proposed changes in the current practice for the incident patients’ treatment assignment. The change concerned increase of the RTx patients’ number by 1% at the expense of the HD patients. The need for improvements in transplantation policies and for better promotion of organ donorship by Greek healthcare authorities is discussed extensively in the subchapter 6.7.
In this study, no primary research was undertaken to estimate the cost of ESRD treatment modality. In order to perform a rough economic estimation of the scenario’s impact, we exploited the only available data for the cost of the different treatments from 2003 (Kontodimopoulos and Niakas 2008). The results have shown net savings of €68.2 million for the period 2009-2020.

Although Monte Carlo techniques are time-consuming, they allow detail simulation of each ESRD patient; thus corresponding statistics can be extracted. In addition to the individual statistics, Monte Carlo techniques allow assessing the uncertainties in the final outcomes by simulating the uncertainties in the input variables, i.e. the incident patients’ assignment to a therapy and variations in the probabilities of the TMs. Therefore, Monte Carlo in conjunction with Markov chain enables analysis of the prevalent ESRD patients’ distribution over model parameters. The developed model is characterised with higher accuracy and reflects more closely the real ESRD patients’ dynamics.
Chapter 8

OUTCOMES AND CONCLUSIONS OF THE STUDY

8.1 CONCLUSIONS

The Markov chain model techniques were used for the prediction of the future ESRD patients’ number in Greece. Two projection models, a Markov chain model and MCMC were developed. The implemented models have proved to be efficient tools for the projection of the future patients’ number and representing ESRD population dynamics. The results of the study show consistency with other international studies.

Both models predicted continuous increase in ESRD prevalent patients’ number in Greece for the period 2010-2020. The demand on resources for the therapy of ESRD patients in 2020 is predicted to be much higher. This will require more human and technological resources together with higher financial expenditures for the Greek health care sector. Alternatively, other treatment modalities such as HHD or Satellite HD and increase in RTx should be considered. At present, HHD, which is
reported to be more cost-effective compared to CHD and PD, is not well introduced in Greece.

The increase in transplant supply would result in less financial expenditures and improvement in patients’ QOL. ESRD treatment methods are considered to be among the most expensive procedures for chronic conditions worldwide with severe impact on patients’ QOL. The results of this study suggest that promoting the idea of transplantation together with creating in every Greek hospital a network of trained professionals responsible for organ procurement and implementing a living kidney donation promotion program, like those in Spain, could significantly improve the situation in Greece. These improvements would include improvement of patients’ QOL and decrease in the financial burden for the health authorities.

8.2 LIMITATIONS OF THE STUDY

There are two types of Markov models used in medical decision making – those in which the state transition probabilities are constant, and those in which the transition probabilities vary over time according to preset regular rules. The first class of models is called Markov chains and was the base for our studies. These models are a subset of more general Markov processes, in which transition probabilities are time dependent. Constant transition probabilities are realistic for diseases with a short time horizon. In most of the chronic conditions there is usually inescapable factor of increasing age. The annual mortality of the healthy population increases exponentially with age. The factor of patients’ ageing was overcome by dividing the patients into three age groups. The condition when incident and prevalent cohorts do not 'age' during the follow-up period is more a theoretical than a practical limitation (Beck and Pauker 1983).

8.3 FUTURE WORK

The proposed model uses Markov chain, which allows estimating QOL and costs of ESRD patients’ treatment. Latest data on quality utilities indexes and ESRD treatment modalities costs in Greece are not available. It is of special interest to apply more recent data on ESRD patients’ treatments costs and patients’ quality measures in order to estimate impact on proposed scenarios of the increase in number of transplantations in the future.
The implemented Markov chain model techniques may be used to evaluate the cost-effectiveness of the development and establishment of HHD as an alternative ESRD treatment, as well as the QOL of these patients. The techniques are also of a special interest to be applied to the CKD patients in Greece in order to evaluate their progress and progression to ESRD.

The approach, presented in the current thesis, is potentially applicable to a broad range of countries and circumstances, because of the minimal data required to implement the techniques. The future work perspective is to apply the proposed methods to project future ESRD patients’ number for other countries.
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Research, design and development of software tools for process management in the area of e-health.


"Results of a living donor kidney promotion program." Transplant Proc 42(8): 2837-2838 (2010/10/26)


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Appendix A

SURVEYS FOR MEASURING HRQOL

The SF-36 is a multi-purpose, Short-Form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Thus, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments (Ware and Sherbourne 1992).

The Kidney Disease Quality of Life (KDQOL) survey was developed in 1994 by the Kidney Disease Quality of Life Working Group as a kidney disease-specific measure of HRQOL. The first version contained the Medical Outcomes Study 36 (MOS SF-36) as a generic chronic disease core, and added items relevant to patients with kidney disease, such as symptoms, burden of illness, social interaction, staff encouragement, and patient satisfaction. Currently, the KDQOL-36 uses the SF-12 (a shorter version of the SF-36) and 24 kidney disease-specific questions (Hays, Kallich et al. 1994).
The **KDQOL-36**, developed by RAND Corporation in 2002, is a reliable and valid 36-item HRQOL survey with five subscales:

**SF-12: Physical Component Summary subscale (Questions 1-12)** and **SF-12: Mental Component summary subscale (Questions 1-12)**, include items about general health, activity limits, ability to accomplish desired tasks, depression and anxiety, energy level, and social activities.

**Burden of Kidney Disease subscale (Questions 13-16)**, includes items about how much kidney disease interferes with daily life, takes up time, causes frustration, or makes the respondent feel like a burden.

**Symptoms and Problems subscale (Questions 17-28)**, includes items about how bothered a respondent feels by sore muscles, chest pain, cramps, itchy or dry skin, shortness of breath, faintness/dizziness, lack of appetite, feeling washed out or drained, numbness in the hands or feet, nausea, or problems with dialysis access.

**Effects of Kidney disease on daily life subscale (Questions 29-36)**, includes items about how bothered the respondent feels by fluid limits, diet restrictions, ability to work around the house or travel, feeling dependent on doctors and other medical staff, stress or worries, sex life, and personal appearance (*Schatell and Witten 2010*).

The **SF-6D** is a classification for describing health derived from a selection of SF-36 items. It is composed of six multi-level dimensions. Any patient who completes the SF-36 or the SF-12 can be uniquely classified according to the SF-6D. The SF-6D provides a means for using the SF-36 and SF-12 in economic evaluation by estimating a preference-based single index measure for health from these data using general population values. The SF-6D allows the analyst to QALYs from the SF-36 for use in cost utility analysis (*Brazier, Roberts et al. 2002*).
Appendix B
DATA ON PATIENTS’ PREVALENCE AND INCIDENCE

The data on patients’ prevalence and incidence for Greece used in the current thesis were obtained from ERA-EDTA annual reports for the years 1998-2009 (ERA-EDTA).

Table B.1 ESRD incident patients’ number by age group and therapy in Greece (1998-2009)

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Table B.1 ESRD incident patients’ number by age group, therapy and in total in Greece (1998-2009)

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Table B.2 ESRD prevalent patients’ number by age group and therapy in Greece (1998-2009)

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<td>5486</td>
<td>8308</td>
<td>755</td>
<td>2235</td>
<td>11298</td>
</tr>
<tr>
<td>2008</td>
<td>1839</td>
<td>4057</td>
<td>5710</td>
<td>8463</td>
<td>764</td>
<td>2379</td>
<td>11607</td>
</tr>
<tr>
<td>2009</td>
<td>1851</td>
<td>4148</td>
<td>6019</td>
<td>8828</td>
<td>761</td>
<td>2429</td>
<td>12018</td>
</tr>
</tbody>
</table>

Table B.4. Incident patients' distribution probabilities by age group and therapy (1998-2009)

<table>
<thead>
<tr>
<th>Year</th>
<th>&lt;45 HD</th>
<th>&lt;45 PD</th>
<th>&lt;45 RTx</th>
<th>45-64 HD</th>
<th>45-64 PD</th>
<th>45-64 RTx</th>
<th>&gt;65 HD</th>
<th>&gt;65 PD</th>
<th>&gt;65 RTx</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>0.87</td>
<td>0.12</td>
<td>0.01</td>
<td>0.88</td>
<td>0.12</td>
<td>0.00</td>
<td>0.89</td>
<td>0.11</td>
<td>0.00</td>
</tr>
<tr>
<td>1999</td>
<td>0.88</td>
<td>0.09</td>
<td>0.03</td>
<td>0.84</td>
<td>0.16</td>
<td>0.00</td>
<td>0.85</td>
<td>0.15</td>
<td>0.00</td>
</tr>
<tr>
<td>2000</td>
<td>0.86</td>
<td>0.09</td>
<td>0.05</td>
<td>0.84</td>
<td>0.16</td>
<td>0.00</td>
<td>0.85</td>
<td>0.15</td>
<td>0.00</td>
</tr>
<tr>
<td>2001</td>
<td>0.83</td>
<td>0.14</td>
<td>0.03</td>
<td>0.88</td>
<td>0.11</td>
<td>0.01</td>
<td>0.89</td>
<td>0.11</td>
<td>0.00</td>
</tr>
<tr>
<td>2002</td>
<td>0.85</td>
<td>0.11</td>
<td>0.04</td>
<td>0.86</td>
<td>0.13</td>
<td>0.01</td>
<td>0.89</td>
<td>0.11</td>
<td>0.00</td>
</tr>
<tr>
<td>2003</td>
<td>0.83</td>
<td>0.13</td>
<td>0.04</td>
<td>0.90</td>
<td>0.10</td>
<td>0.00</td>
<td>0.90</td>
<td>0.10</td>
<td>0.00</td>
</tr>
<tr>
<td>2004</td>
<td>0.87</td>
<td>0.07</td>
<td>0.05</td>
<td>0.86</td>
<td>0.13</td>
<td>0.01</td>
<td>0.91</td>
<td>0.09</td>
<td>0.00</td>
</tr>
<tr>
<td>2005</td>
<td>0.91</td>
<td>0.06</td>
<td>0.03</td>
<td>0.89</td>
<td>0.11</td>
<td>0.00</td>
<td>0.91</td>
<td>0.09</td>
<td>0.00</td>
</tr>
<tr>
<td>2006</td>
<td>0.81</td>
<td>0.14</td>
<td>0.05</td>
<td>0.91</td>
<td>0.09</td>
<td>0.00</td>
<td>0.92</td>
<td>0.08</td>
<td>0.00</td>
</tr>
<tr>
<td>2007</td>
<td>0.81</td>
<td>0.11</td>
<td>0.08</td>
<td>0.89</td>
<td>0.10</td>
<td>0.01</td>
<td>0.91</td>
<td>0.09</td>
<td>0.00</td>
</tr>
<tr>
<td>2008</td>
<td>0.81</td>
<td>0.15</td>
<td>0.04</td>
<td>0.88</td>
<td>0.12</td>
<td>0.00</td>
<td>0.92</td>
<td>0.08</td>
<td>0.00</td>
</tr>
<tr>
<td>2009</td>
<td>0.86</td>
<td>0.13</td>
<td>0.01</td>
<td>0.81</td>
<td>0.17</td>
<td>0.01</td>
<td>0.94</td>
<td>0.06</td>
<td>0.00</td>
</tr>
</tbody>
</table>
Table B.5 Renal transplants performed during the period 2002-2009 in Greece by donor type in numbers (N) and percentages (%)

<table>
<thead>
<tr>
<th>Year</th>
<th>Living donor</th>
<th></th>
<th>Deceased donor</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>2002</td>
<td>89</td>
<td>42.0</td>
<td>124</td>
<td>58.0</td>
<td>213</td>
</tr>
<tr>
<td>2003</td>
<td>88</td>
<td>38.0</td>
<td>141</td>
<td>62.0</td>
<td>229</td>
</tr>
<tr>
<td>2004</td>
<td>78</td>
<td>39.0</td>
<td>123</td>
<td>61.0</td>
<td>201</td>
</tr>
<tr>
<td>2005</td>
<td>86</td>
<td>33.2</td>
<td>173</td>
<td>66.8</td>
<td>259</td>
</tr>
<tr>
<td>2006</td>
<td>92</td>
<td>37.9</td>
<td>151</td>
<td>62.1</td>
<td>243</td>
</tr>
<tr>
<td>2007</td>
<td>125</td>
<td>52.5</td>
<td>113</td>
<td>47.5</td>
<td>238</td>
</tr>
<tr>
<td>2008</td>
<td>71</td>
<td>26.8</td>
<td>194</td>
<td>73.2</td>
<td>265</td>
</tr>
<tr>
<td>2009</td>
<td>35</td>
<td>20.8</td>
<td>133</td>
<td>79.2</td>
<td>168</td>
</tr>
</tbody>
</table>
The model used least squared estimator method in order to estimate TM for ESRD population in Greece, based on TM for other countries presented in national and international publications. The transitions of the ESRD patients were established within four TM states: HD, PD, RTx and Death. The obtained values of the transition probabilities of the ESRD patients are presented in Table C.1, including name of the author(s) who conducted the study, period based on which the transition probabilities values were estimated and age group. At first all the available TMs values were obtained from the literature, then based on these values upper and lower bounds were constructed and then the confidence interval was added.

*Vestergard and Lokkegaard (1997)* have created Markov chain model for the age groups <60 and >60 years old (*Vestergaard and Lokkegaard 1997*). The transition probabilities available were obtained from the observations for Denmark for the period 1991-1995.
Table C.1. Values of transition probabilities obtained from the national and international literature (n/a – not available)

<table>
<thead>
<tr>
<th>Author and country</th>
<th>Year</th>
<th>Age group</th>
<th>Transition probabilities values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vestergaard and Lokkergaard</td>
<td>1991-1995</td>
<td>&lt;60</td>
<td>HD n/a 0.090-0.170 n/a 0.120-0.170</td>
</tr>
<tr>
<td>Denmark</td>
<td></td>
<td></td>
<td>PD 0.240-0.330 n/a n/a 0.010-0.110</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RTx 0.030-0.040 0.010-0.040 n/a 0.020-0.040</td>
</tr>
<tr>
<td>Vestergaard and Lokkergaard</td>
<td>1991-1995</td>
<td>&gt;60</td>
<td>HD n/a 0.060-0.150 n/a 0.160-0.230</td>
</tr>
<tr>
<td>Denmark</td>
<td></td>
<td></td>
<td>PD 0.110-0.240 n/a n/a 0.200-0.300</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RTx 0.010-0.030 0.000-0.010 n/a 0.060-0.120</td>
</tr>
<tr>
<td>Kirby and Vale</td>
<td>first year of the treatment</td>
<td></td>
<td>HD 0.925-0.939 n/a n/a 0.001-0.015</td>
</tr>
<tr>
<td>England</td>
<td></td>
<td>total ESRD population</td>
<td>PD n/a n/a n/a n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RTx n/a n/a n/a n/a</td>
</tr>
<tr>
<td>Ioannidis</td>
<td>2000</td>
<td></td>
<td>HD 0.842 0.008 0.019 0.132</td>
</tr>
<tr>
<td>Greece</td>
<td></td>
<td>total ESRD population</td>
<td>PD 0.056 0.737 0.018 0.190</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RTx 0.028 0.001 0.954 0.017</td>
</tr>
<tr>
<td>Teerawattananon</td>
<td>2007</td>
<td>total RRT population</td>
<td>HD n/a 0.0064 n/a n/a</td>
</tr>
<tr>
<td>Japan</td>
<td></td>
<td></td>
<td>PD 0.027 n/a n/a n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RTx n/a n/a n/a n/a</td>
</tr>
<tr>
<td>Finish Renal Registry</td>
<td>2002-2008</td>
<td>total ESRD population</td>
<td>HD 0.597-0.699 0.042-0.063 0.063-0.129 0.178-0.213</td>
</tr>
<tr>
<td>Finland</td>
<td></td>
<td></td>
<td>PD 0.160-0.221 0.378-0.491 0.139-0.246 0.122-0.210</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RTx 0.010-0.018 0.003-0.006 0.844-0.959 0.023-0.133</td>
</tr>
<tr>
<td>Schaubel et al.</td>
<td>12-18 month of the treatment</td>
<td>45-65</td>
<td>HD 0.868 0.008 0.074 0.049</td>
</tr>
<tr>
<td>Canada</td>
<td></td>
<td></td>
<td>PD 0.055 0.848 0.053 0.044</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RTx 0.016 0 0.977 0.008</td>
</tr>
</tbody>
</table>
Kirby and Vale (2001) performed projections of the ESRD patients in England. The transition probabilities available from this study were for the total ESRD population. Minimum and maximum values of transition probabilities are for the first year of the treatment (Kirby and Vale 2001).

According to the publication of Ioannidis (2002), transition probabilities for the total ESRD population in Greece for the year 2000 were calculated based on the available net transitions (Ioannidis, Papadaki et al. 2002). The total ESRD population includes transitions of the total prevalent ESRD patients not divided by age group. Based on the net transitions the rates were calculated and then transformed into probabilities by Eq. 4-7 (Beck and Pauker 1983).

The transition probabilities obtained from the publication of Teerawattananon, represent ESRD population transition in Japan for 2007 (Teerawattananon, Mugford et al. 2007).

Finnish Renal Registry published net transitions of the total Finnish ESRD population for the years 2002-2008. The transition probabilities were calculated and then the results were combined into a minimum and maximum values range (FRKD 2001-2008).

Schaubel et al. (2000) in his work has presented transition probabilities for the age group 45-65 for period between the 12th and the 18th month of the treatment for Ontario, Canada (Schaubel, Morrison et al. 2000).