Treatment decisions in elderly patients with end-stage renal disease

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Treatment decisions in elderly patients with end-stage renal disease

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van Prof. dr. A.C. Nieuwenhuijzen Kruseman,
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Wubbo Mulder

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What if a day or a month or a year
Crown thy delight with a thousand wished contentings,
Cannot the chance of a day or an hour
Fill thee again with as many sad tormentings

English Hymn

Wat (betekent het) als een dag of een maand of een jaar
Uw verrukking bekroont met duizend gewenste bevredigingen?
Kan niet het toeval van een dag of een uur
U niet opnieuw plagen met evenveel droeve kwellingen?

Engelse Psalm

Aan: mijn ouders

Contents

Abbreviations

ADL	=	Activities of daily living
ACE	=	Angiotensin converting enzyme
ACTH	=	Adreno cortico tropic hormone
ARF	=	Acute renal failure
BOP	=	Beoordelingsschaal ouderen patiënten (Assessment scale elderly patients)
CAPD	=	Continuous ambulatory peritoneal dialysis
Ccr	=	Creatinine clearance rate
CI	=	confidence interval
CVD	=	Cardiovascular disease
EDTA	=	European dialysis and transplant association
ERA	=	European renal association
ERPF	=	Effective renal plasma flow
ESRD	=	End-stage renal disease
GFR	=	Glomerular filtration rate
HD	=	Hemodialysis
ICD-9-CM	=	International classification of diseases 9th revision, clinical modification
IDDM	=	Insulin-dependent diabetes mellitus
MMSE	=	Mini mental state examination
MOF	=	Multi organ failure
NIDDM	=	Non-insulin-dependent diabetes mellitus
NSAIDs	=	Nonsteroidal anti-inflammatory drugs
PAH	=	Para amino hippuric acid
PD	=	Peritoneal dialysis
RAAS	=	Renin angiotensin aldosterone system
RRT	=	Renal replacement therapy
RPF	=	Renal plasma flow
SD	=	Standard deviation
SIP68	=	Sickness impact profile (The Maastricht variant of the SIP with 68 questions)
USRDS	=	United States renal data system

Chapter 1

Introduction, general outline and aims of the thesis

WJ Mulder

Introduction, general outline and aims of the thesis

End stage renal disease (ESRD) is more and more a disease of elderly people. The progress of medical technology not only leads to an increase of average life expectancy, but also to a more effective treatment of cardiovascular disease. This results in a growing number of patients with ESRD as a late manifestation of vascular disease. Moreover, medical progress enables us to enroll patients at advanced age in renal dialysis and transplantation programs, whereas until recently the decline of physiology and function in the elderly were considered contraindicative for renal replacement therapy (RRT).
RRT is a heavy burden for the elderly patient, who has to undergo therapy for many hours a week and has to withstand many side effects and complications. Elderly patients on dialysis often have more chronic illnesses and are more debilitated than those without renal failure and are therefore more prone to complications. RRT is a very expensive form of treatment and therefore also a heavy burden for society.
For elderly patients, RRT (dialysis, mostly passive center dialysis) is mostly lifelong therapy, because renal transplantation is a scarce option.
In most West-European countries, as well as in the USA, and Australia, some form of selection is applied for the elderly patients with ESRD entering RRT-programs. Hardly any data can be found in literature which criteria are used to carry out this selection. Although there is general consent that severe loss of cognitive function is a selection criteria for not entering RRT programs, whereas age itself is not. Other factors like general condition of the patient, co-morbidity, but also socioeconomic status, social activity, and finally the limitation in the health care resources, probably all play a roll in making the decision to offer renal replacement therapy in the individual elderly patient. How each of these and perhaps other factors influence patient selection is largely unknown.
Dialysis therapy is no cure for ESRD, but a therapeutic measure to sustain life. The ESRD patient on dialysis is a patient with a chronic disease, which influences many aspects of his life. A number of studies demonstrate significant changes in the quality of life of almost every patient on RRT[1,2,3].
In the USA, with probably less patients excluded from RRT programs, a large percentage of elderly patients withdraw from therapy, indicating the high demands of dialysis on the individual patient. On the other hand, there is an indication that some elderly patients are able to adjust to stressful events such as RRT[4]. So in many respects it is useful to find the best match between patient and therapy.

In this thesis we will try to find an answer to a number of questions concerning this subject (Figure 1.1).
First of all we undertook a retrospective study to answer the question whether there is selection of elderly patients in the Netherlands for entering RRT programs and to determine the percentage of elderly ESRD patients who do not receive RRT.

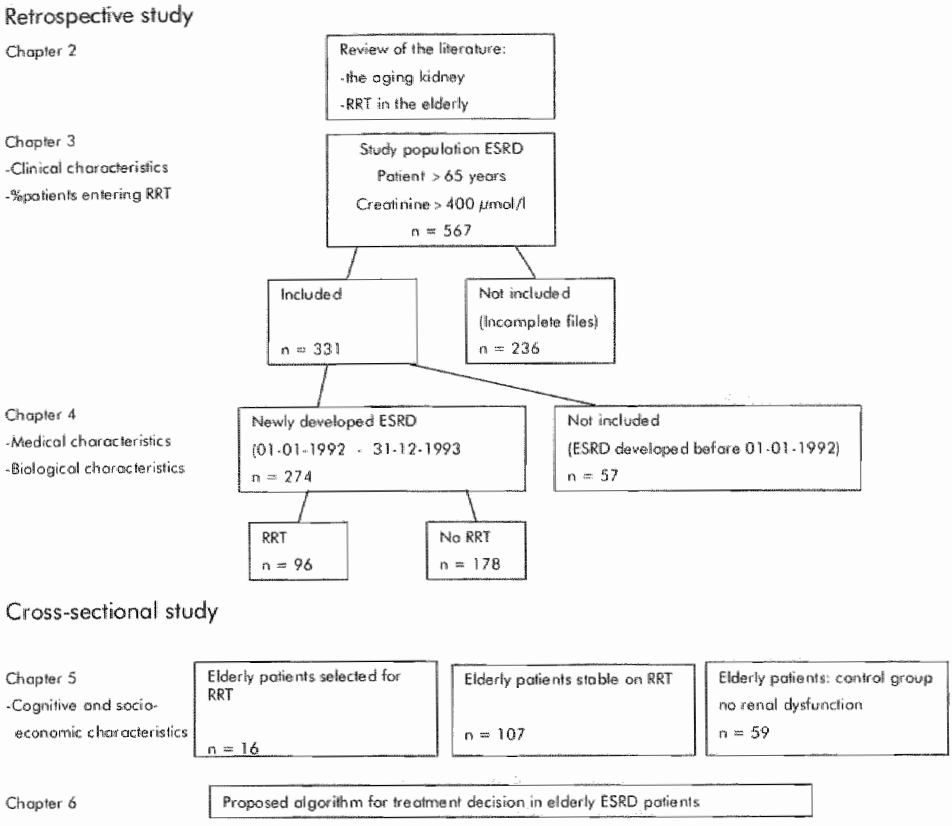

Figure 1.1 General outline of the thesis

Secondly we wanted to find out which criteria can be used to identify those elderly patients with ESRD who will respond best on RRT.
In an elderly population sickness is more often one of the problems contributing to a complex problem of multimorbidity and functional loss, than a single entity. Therefore, our investigations focused on somatic, biological, aspects as on social, non-biological, factors.
A question of equal importance was whether the elderly ESRD patient benefits from RRT. Is chronic dialysis just adding time to life or offers it the patient an opportunity for a meaningful continuation of his life?

In chapter 2A the literature is reviewed concerning morphological and functional changes of the aging kidney, as well as the pathological conditions leading to loss of renal function in the elderly.
In chapter 2B a literature review is performed on renal replacement therapy in elderly patients, differentiated to the respective treatment modalities, with inclusion of data on renal transplantation in this population.

In chapter 3 a retrospective study is presented in which epidemiological data are collected of elderly patients with ESRD in 1992 and 1993, seen in four hospitals with dialysis facilities in the southern part of the Netherlands. Patient selection was performed by a survey in the laboratory records of the four participating hospitals. Elderly patients age 65 years and over, with a serum creatinine of 400 μmol/l, as an arbitrary measure of ESRD, were selected. In this way we found 567 patients. The medical files of 331 patients revealed sufficient data for data collection on baseline characteristics, socioeconomic status, functional status, medical history, primary renal diagnosis, comorbidity, medical interventions, and clinical course. Of special interest in this study is the fact that data are collected not only from patients who were actually treated for ESRD, but also those patients are taken in account who, based on their laboratory results were potentially candidates for RRT, but did not receive dialysis treatment. In this way a rather accurate estimation was possible of the size of the problem of ESRD in the elderly. The focus in this chapter is on the clinical characteristics of elderly patients with end-stage renal disease.

In chapter 4 a retrospective study is presented on the medical and biological characteristics of the same population. However in this study only data of 277 elderly patients who developed ESRD in 1992 and 1993 were collected. A comparison is made between patients who underwent RRT and patients who did not. Apart from a survival analysis between both groups, an attempt is made to find out which biological and non-biological criteria were decisive in the treatment decision.

In chapter 5 biological and non-biological characteristics of elderly patients with ESRD are studied in a cross-sectional study. A comparison is made between patients with end-stage renal disease but not yet on RRT, patients stable on RRT and elderly patients with no apparent renal dysfunction. In this chapter the hypothesis is tested that RRT is improving the condition and the feeling of well being of elderly patients with ESRD. Also the question is posed whether, and if so in which respect, patients stable on RRT still differ in their assessment of sickness from elderly patients with no renal impairment.
In this chapter non-biological characteristics are central issues. Assessment of the cognitive function and the socio-economic status was performed in a cross-sectional study. In a retrospective investigation measuring of cognitive function and social activity is not good feasible, so a transversal investigation was necessary. A comparison was made between 16 elderly patients with ESRD before undergoing RRT, 107 patients stable on RRT and 59 consecutive patients, without important renal impairment and in no need for longstanding chronic therapy referred to the outdoor geriatric department. Beside cognitive function, measured by the Mini Mental State Examination (MMSE), and functional status using the Katz's scale of basic activities and the Barthell index, quality of life was registered with the aid of the Maastricht variant of the Sickness Impact Profile, the SIP68 in this study.

Two questions are addressed in this chapter. First, are cognitive function, socio-economic status, social activity, and patients self-estimation of quality of live, factors in patient selection for RRT; and, secondly, are patients on RRT improving on these factors during RRT. The geriatric outdoor population is here used as a control group to assess the basic functional and socio-economic parameters in a elderly population for comparison.

In chapter 6 we discuss the ethical implications of selection of elderly patients for treatment by renal function replacement therapy. Secondly we propose an algorithm, which can be used to perform this selection.

In chapter 7 a summary is given of the studies in this thesis.

Chapter 8 is a summary in Dutch.

In summary, the main questions of this thesis are:

1. What is the incidence and prevalence of ESRD in elderly patients? (Chapter 3)
2. What is the extent of patient selection for renal replacement therapy in the group elderly patients with ESRD? (Chapter 3)
3. Are there biological and/or non-biological determinants on which this selection is based? (Chapter 4)
4. What is the outcome of RRT in elderly patients, in comparison with the patients not treated with RRT? (Chapter 3)
5. What are the biological characteristics of elderly patients with ESRD at the start of treatment? (Chapter 5)
6. Is RRT in elderly patients leading to improvement of quality of life and social activity? (Chapter 5)
7. Is it possible to make recommendations for future patient selection? (Chapter 6)

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Chapter 2A

Renal function and renal disease in the elderly

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Abstract

In all industrialized countries, life expectancy has risen in the past 100 years. The number of elderly patients reaching end-stage renal disease (ESRD) and requiring renal replacement therapy has also increased. During the past few decades, the pattern of ESRD has changed significantly with the emerging predominance of elderly patients. The causes of this phenomenon are manifold and include an increasing number of chronic diseases typical of the 'third age', such as type 2 diabetes and vascular disease. In many species, a consequence of aging includes deterioration of renal function, partly due to structural alterations, and partly as the result of a diminishing blood flow. In humans, the aging kidney is characterized by modifications resulting from organic and functional disturbances. In particular, type 2 diabetes mellitus has emerged as an important condition, the microvascular and macrovascular complications of which are a common cause of morbidity and mortality in older patients. In part I of this review, the morphological and functional changes of the aging kidney will be reviewed, as well as the pathological conditions leading to the loss of renal function in the elderly.

1. The aging kidney

1.1. Introduction

Today, the treatment of renal diseases reflects a changing situation with an aging population. The proportion of the population made up of elderly persons in the western world is steadily increasing. In 1900, only 4% of the population in the Netherlands was 65 years of age or older. In 2000, the percentage of persons 65 years or older has increased to 13.5, representing 2.1 million inhabitants. Moreover, 2.3% of the Dutch population is 80 years of age and older.[1]

The growing elderly population is a consequence of increased longevity in our society. The life expectancy for men was 70.8 years in 1972; this increased to 75.2 years in 1997. For women, it was 76.8 years in 1972 and 80.6 years in 1997.[2]
Longevity and an increasing elderly society have several implications for the delivery and costs of health care in patients with renal disease. Elderly persons use health care services at a greater rate than young persons do. Health care and the costs associated with it increase with age.[3,4] The major reason for this increase is the improvement in medical technology which allows effective treatment for elderly patients. Age itself is no longer a contraindication for even complex medical treatments such as hemodialysis and renal transplantation.
Since the 1980s, renal replacement therapy is technically available to older patients. Since then an increase is seen in renal replacement therapy in elderly patients due to a liberalisation of acceptance criteria for dialysis in combination with the age-related increase in the incidence of chronic renal failure.[5] However, *in daily practice, renal* replacement treatment is only performed in approximately 40% of elderly patients with renal failure.[6-12] Comorbidity, impaired mobility and impaired cognitive functions are the main medical criteria for selecting elderly patients for renal replacement therapy.[13,14] Yet, ageism and different opinions of patients, of primary care physicians and of specialists are involved in the selection process.[15,16]
Giving the important implications of age on health care for elderly patients with renal disease, we reviewed the main aspects of the pathophysiology of the aging kidney, the epidemiology of renal failure at old age, and the application of renal replacement therapy in the elderly.

1.2. The aging kidney

Aging is accompanied by a substantial reduction in renal function. Yet, the function of the senescent kidney is still sufficient under normal circumstances at older age. Changes in renal function reduce the capacity of elderly persons to respond to physiological and pathological stress. In fact, a number of serious

characteristic morphological and functional disturbances often characterize the aging kidney.

1.3. Morphological changes

1.3.1. Macroscopic changes

The weight of the human kidneys remains fairly constant until the fifth decade of life and then slowly decreases to less than 300 g in the ninth decade of life.[17-19] There is a more substantial loss of tissue in the cortical than in the medullar region.[20,21] In the medulla an increase is seen in the interstitial tissue, accompanied by fibrosis and increase of fat content at the level of the renal sinus. Renal length may diminish as much as 2 cm between the fifth and eight decade, which represents a loss in volume of 40%.[22] This reduction correlates with the degree of sclerosis of the intrarenal arteries, suggesting that these age-related changes are related to atherosclerosis.
In elderly persons without apparent renal disease, over 50% of the kidneys autopsied are smooth or manifest only a fine granularity at the surface. Only about 12 to 14% of the kidneys are coarsely scarred.[23,24] This scarring is ubiquitously distributed over the kidney. Studies of hypertensive subjects have shown similar results.
Simple cysts are common in the aging kidney, especially along the distal nephron. They increase in frequency and size after the fifth decade.[25]
As the cortex becomes thinner, glomeruli tend to crowd together.[26] The medulla shows a marked increase in interstitial fibrosis after the age of 70.[27]
A reduced concentration of acid mucopolysaccharides in the medulla is mentioned as a cause of this medullar fibrosis. In the cortex, these concentrations remain unchanged.[28]

1.3.2. Microscopic changes

1.3.2.1. The glomeruli

The number of glomeruli decreases with age. Moore found that the mature adult kidney contains between 600.000 and 1.2 million glomeruli.[29] In subjects dying in the seventh decade of their lives the number of glomeruli was half or two-thirds of that at a younger age. After the third decade, glomerular sclerosis begins to appear, eventually leading to collapse of glomeruli, which are finally replaced by hyaline material. The proportion of hyalinized, obliterated glomeruli in the adult kidney tends to increase with age, especially in men. In an autopsy study, Kasiske showed that glomerulosclerosis correlates with the extend of intrarenal vascular changes.[30] Both age and the extend of atherosclerotic vascular changes correlated independently with the number of hyalinized glomeruli in the cortex as well in the medulla. In subjects over the age of 50, this proportion ranges from 1 to 30% and is unrelated to the total number of glomeruli[26,27]. While the number of glomerular tufts, as well as the number of glomerular and tubular cells decreases, the size of the individual cells

increases.[31] In juxtaglomerular nephrons this obliteration leads to a direct continuity between afferent and efferent arterioles.[32] In the more peripherally sited nephrons, obliteration of the glomeruli is accompanied by an obliteration of the vasa afferentia.
In rats, the earliest changes in glomerular sclerosis include thickening of the mesangium and of the glomerular basal membrane. Changes in the number of mesangial cells and in the contents of glomerular cells lead to obliteration of the urinary space, adhesion of the capillary loops, hyalinisation and, finally, sclerosis.[33] The glomeruli of aging rats contain IgM, but these deposits do not seem to produce the renal lesions.[34] The appearance of these deposits coincides with the development of proteinuria and the frequency of both increases with age. In humans, the glomerular basement membrane thickens only until the fourth decade.[35] After the age of 60, the surface area of the glomerular basement membrane decreases again and shows wrinkling, followed by deposition of hyaline material. With the reduction in the number of glomeruli, hyperperfusion and hyperfiltration of the remaining glomeruli develop.[36] Hyperfiltration leads to disruption of the capillary membranes contributing to progression of the sclerosis of the glomeruli.

1.3.2.2.The distal nephron

The tubuli show marked changes with increasing age: thickening of the basement membrane, focal cellular necrosis, irregular cell height, and morphological cell alterations, all eventually leading to a decrease in the proximal tubular volume.
Collecting tubules dilate and resemble diverticuli, many of which contain bacteria and may be the source of recurrent urinary tract infections in the elderly.[37] These ectasia and diverticuli from distal and convoluted tubules become more common with age. From one single nephron up to 20 may arise and probably result in the weakening of the tubular basement membrane. Many contain histological evidence of casts, epithelial debris and organisms, leading some authors to suspect that they are responsible for recurrent urinary tract infections.[38] In biopsies drawn from over 100 patients - from newborn to very old subjects - a strong correlation was found between glomerular and tubular dimensions. The volume of glomeruli and proximal tubuli diminished at the same rate. Oliver, however, stated that in later life there is little correlation between the size of glomeruli and tubuli. Thus the tubule does not constantly degenerate after glomerular destruction.[39] He described hypertrophy with hyperplasia of proximal tubules of glomeruli that were normal in size, atrophied, or even destroyed. More distal parts of the nephron were much less affected.

1.3.4. Risk factors

It is still a matter of debate whether the loss of nephrons is the result of aging alone or an effect of concomitant pathological conditions such as hypertension, diabetes mellitus type I as well as type II, recurrent infections of the urinary tract, hyperlipidemia, and atherosclerosis.[40] Cigarette smoking increases both in type I and in type II diabetes mellitus the risk of development of nephropathy and

nearly doubles the progression to end-stage renal failure.[41,42] But also in patients with a primary renal disease smoking is an independant risk factor for progression to renal failure.[43] The pathogenesis is thought to be vascular, with intra- en extrarenal hemodynamic changes, and non-vascular, toxic, with damage of the renal and particularly glomerular microvasculature as a result of its effects on platelet function, thromboxane metabolism and endothelial cell function.[44]
Renal irradiation and thyroid or androgen supplements are mentioned to accelerate age-related glomerular sclerosis.[45-47]
The process of glomerulosclerosis may be influenced to some extend by therapies aiming at decreasing glomerular and systemic hypertension, reducing hyperfiltration by decreasing protein load and preventing secondary hyperparathyroidism.[48,49]

1.4. Vascular changes and renal plasma flow

1.4.1. Vascular changes

Renal blood flow per gram decreases progressively after the fourth decade.[50] Cortical flow decreases to a greater extend than medullary flow. This decline is not attributable to a reduced cardiac output, but due to an increased renal vascular resistance.[51]
The small arteries of the kidney show an age-related progressive thickening of the intima, mainly consisting of elastic tissue, associated with atrophy of the media.[27]
In the terminal arteries and in the arterioles, intimal thickening is caused by subendothelial deposition of hyaline material and collagen fibers. Changes appear in small arteries as early as the second decade but become more pronounced after the age of 30. By the age of 50 all arteries are involved.[52]
The question remains whether these changes are the result of aging alone or (partly) of hypertension and atherosclerosis. In a micro-angiographic examination of the aging normotensive kidney, Ljungqvist and Lagergren, who recorded increasing tortuosity of the afferent arterioles, did not find a difference between the ages of 60 and 79.[53]
Postmortem angiographic examination of kidneys of normotensive subjects showed the most severe changes in the most peripheral arteries, particularly those at the renal poles. However, no correlation was found between age and severity of vascular changes above the age of 50. Only a comparison between young and elderly subjects gave significant differences.[23,54]
Aging also has its influence on the endothelium function in the renal circulation. Intravenously administrated L-Arginine induces a much smaller increase in renal plasma flow and plasma cGMP in hypertensive patients than in normotensives.[55] Multivariate analysis however showed that aging besides hypertension may independently impair endothelium-dependent renovascular dilatation. This effect is believed to be caused, at least in part, by a decrease in nitric oxide production.

1.4.2. Renal plasma flow

Ageing is accompanied by a decrease of renal plasma flow (RPF) and renal blood flow.[56] Renal plasma flow (RPF), measured by para-amino-hippuric acid-(PAH-)clearances, decreases with age at a greater rate than inulin clearance, from a mean of 649 ml/min in the fourth decade to a mean of 289 ml/min in the ninth decade. The increment of the RPF on an acute oral protein load (1g/kg body weight) is also reduced in elderly (>60 years) patients.[57] McDonald and colleagues found that elderly subjects were capable of a greater vasodilatation (and a greater increase in PAH) than younger subjects.[58]
They suggested that renal vasculature in elderly people showed a relatively higher state of vasoconstriction. The decrease in RPF, they stated, was, therefore, the result of an enhanced renal vascular resistance. Later investigations, however, showed a greater baseline vasodilatation in the renal vasculature of the elderly.[59] This postulates a diminished blood flow to the renal vessels due to intraluminal changes (atherosclerosis). The rise in blood pressure with age and the high-protein 'western' diet are mentioned as possible contributors to the progressive fall in renal perfusion and function with increasing age. However a comparison between 29 inhabitants of Boston (USA) (age range 19- 79 years, mean: 52.4) and 16 indian inhabitants of an isolated Panamanian island (age range 18-86 years mean: 51.6) with no tendency of blood pressure rise with age and on a low protein diet, does not support this hypothesis.[60] Renal plasma flow and filtration fraction (GFR/effective RPF) rose with age in both populations and even steeper in the indian population. GFR however, was higher at any age in the island inhabitants.
The cortical blood flow decreases more rapidly than the mean blood flow, sparing the juxtamedullary nephrons. These nephrons have a higher filtration fraction. This seems to explain why the filtration fraction in the elderly is often increased.[61] However, this can also indicate an increased postglomerular vascular resistance.

1.5. Functional changes in aging

1.5.1. Glomerular filtration rate

Glomerular filtration rate (GFR) is low at birth, reaches normal (adult) values before the end of the second year of life, and remains fairly constant until the age of 30.[62] Early studies indicate that, thereafter, GFR shows a linear decline. As a result, the values in the eighth decade are only one-half to two-thirds of those measured in young adults.[41,63]
Later investigations suggest that the decline in GFR with increasing age shows more of a non-linear pattern.[64-67] The decline of GFR in younger adults has an average rate of 4 ml/min per decade. In the period between 50 and 75 years of age, this rate amounts to approximately 10 ml/min per decade.[68] After the age of 75, the rate of decline decreases again to a slower rate.[69]
Yet, while creatinine clearance decreases with age, often no increase in plasma creatinine is seen.[70] Thus, serum creatinine concentration in the elderly conceals the physiological decrease in GFR. In renal disease, it is usually thought that the

number of nephrons must be halved before function is affected, a reduction apparently unusual in the aging kidney.[71] The remaining nephrons probably undergo compensatory hypertrophy.[72] Differences between kidneys in this capacity for hypertrophy, possibly depending on the condition of their vessels, could explain the large differences in glomerular dimensions found in the elderly.[71] Comorbid conditions therefore, can confound renal function in the elderly. Fliser et al. performed a comparative study between young healthy normotensive subjects (n=24 mean age 26.3 years), elderly healthy normotensive subjects (n=29 mean age 68.7 years), elderly treated and untreated hypertensive patients (n=25 mean age 70.6 years), and elderly patients with compensated mild to moderate heart failure (n=14 mean age 69.6 years).[73] Compared to the young subjects mean GFR was significantly lower in the elderly, despite similar mean plasma creation levels.
However, GFR was in normal range in the elderly normotensive and hypertensive subjects, but not in the elderly patients with heart failure. ERPF was significantly lower in the elderly hypertensive patients in comparison with the normotensive elderly and still lower in the heart failure patients. Mean renovascular resistance and filtration fraction were significantly higher in the elderly, particularly in hypertensive and heart failure patients as compared with the young.

Despite the decrease in GFR in the course of a person's life, renal reserve, defined as peak postprandial GFR minus basal GFR, remains unchanged with increasing age.[74] Population studies demonstrate a 10% decrease in GFR per decade after the age of 40, without a change in serum creatinine.[75]
Because of the limited use of serum creatinine to estimate the creatinine clearance (Ccr) in the elderly, the Cockroft and Gault formula is often used to calculate it.[76]

$$\text{Men} \qquad Ccr = \frac{\{140 - \text{age (years)}\} \times \text{body weight (kg.)}}{72 \times \text{serum creatinine mg/dl}}$$

Women Multiply male Ccr by 0.85

Conversion factor SI Units to mg/dl: 11.31

Although this formula is useful to estimate Ccr, one must realize that it is not a substitute for careful clinical evaluation of the (elderly) patient.[77] Gentric and colleagues found that the Cockroft and Gault formula underestimated GFR when compared to isotopic measurements in well-nourished patients with stable

renal function who were 81-96 years of age.[78] A study using iothalamate clearance as the gold standard in 41 patients aged 65-85 years found a poor correlation with the estimation of Cockroft and Gault.[79]
Longitudinal studies show a very large individual variance in the correlation between age and Ccr. Lindeman et al. performed a long-term follow-up study of 446 persons, divided into three groups. Group 1 included 118 patients with some kind of renal disease - infection, hematuria, proteinuria, kidney stones, glomerulonephritis, or obstruction, group 2 consisted of 74 patients with hypertension, and group 3 included 254 healthy subjects.[80] In all three groups, the mean decline in Ccr was 0.87 ml/min per year: in group 1 it was 1.1 ml/min per year, in group 2, 0.92 ml/min per year; and in group 3, 0.75 ml/min per year.
Of these 446 persons, one-third (156) showed an increase in their GFR, suggesting that the decline in GFR often found in seemingly healthy persons is the result of an undetected pathological condition.

1.5.2. Sodium and potassium metabolism

With increasing age the capacity of the kidneys to conserve sodium becomes impaired. Frequently elderly patients have a high natriuresis and tend to sodium depletion, despite a decrease in GFR.[81] Possible causes for renal sodium loss in healthy aged subjects include a low aldosterone level and a diminished reabsorption function of the ascending Henle's loop.[82] Reduced Na-K-ATP-ase activity may also be involved.[83] Acute sodium loading is associated with an enhancement of sodium excretion. In the elderly however, this reaction is delayed in comparison to younger subjects.[84]

Elderly persons have lower plasma renin activity. Basal renin, whether estimated by plasma renin concentration or renin activity, is diminished by 30%-50% in the elderly, despite normal levels of renin substrate. This basal difference between young and old individuals is magnified by manoevres that augment renin secretion, eg salt restriction, diuretic administration and upright position.[85]
The lowered renin levels are associated with 30%-50% reductions in plasma concentrations of aldosterone, as well as with significant reductions in the clearance rate and the urinary aldosterone excretion, while on an unrestricted salt diet as well as after salt restriction.[86,87] Plasma aldosterone and cortisol responses after ACTH stimulation are not impaired with advancing age, demonstrating that aldosterone deficiency in the elderly is a function of the coexisting renin deficiency and is not secondary to intrinsic adrenal changes. This probably accounts for the impaired salt restriction in elderly patients when challenged with a low-salt diet. Similarly it would account for the tendency of elderly subjects to develop hyperkalemia when placed on a low-salt diet. Age-related alterations of the kidney (glomerulosclerosis, decreased number of functional nephrons) might account for the difference in the active to inactive plasma renin ratio. Also, a diminished synthesis of angiotensinogen by the liver can contribute to the decrease in the activity of the RAAS in aging. Furthermore,

aging is associated with a reduced adrenal responsiveness to angiotensin II, resulting in a lower production of aldosterone.[88]
The capacity to conserve potassium is also diminished in the elderly. Total body potassium is 20% lower than in younger subjects.[89] On the other hand can the age-related decreases in renin and aldosterone contribute to an increased risk for hyperkalemia in the elderly in a variety of clinical settings. Through its action on the distal renal tubule, aldosterone increases Na^+-reabsorption and facilitates the excretion of potassium. Aldosterone is therefore one of the major protective mechanisms in the prevention of hyperkalemia during potassium challenge. Since GFR (another major determinant of potassium excretion) is also impaired in older patients, serious elevations in plasma potassium are likely to develop, especially in the presence of GI bleeding or when potassium salts are given intravenously. Moreover, the tendency to hyperkalemia is enhanced by any clinical setting associated with acidosis since the senescent kidney is rather slow in its reaction to acid loading, resulting in prolonged depression of serum pH and concomitant potassium elevation.
Potent antagonists of renal potassium excretion (e.g., spironolactone or triamterene), as well as most nonsteroidal anti-inflammatory drugs (NSAIDs), ß-adrenergic blockers, and angiotensin- converting enzyme (ACE) inhibitors, which also inhibit potassium elimination, should be administered with caution in the elderly, and the concomitant administration of these agents and potassium should be avoided.[90]

1.5.3. Calcium and phosphate metabolism

The serum levels of serum electrolytes, including calcium and phosphate remain relatively stable during life. The aging kidney, however, has a reduced capacity to deal with drastic changes in the serum levels of different electrolytes.[91] For example, in the elderly, the reaction to immobilization, particularly when due to paralysis or a fracture, is exaggerated and may rapidly produce urinary calcium excretion in excess of 500 mg/24 h and lead to calcium stone formation.
It is customary to find relatively lower normal serum levels of calcium and higher serum levels of phosphate in the elderly as compared to young adults. In the aged, hypocalciuria and hyperphosphaturia are often found, the result of functional renal impairment.[92]
In addition, it should be noted that the elderly can suffer from a variety primary and secondary renal diseases that profoundly influence the renal metabolism of calcium and phosphate: e.g. Paget's disease, hyperthyroidism, malignancies, vitamin D deficiency, hyperparathyroidism, and diabetes mellitus.[93,94]

1.6. Risk factors

1.6.1. Diabetes mellitus

Over the past two decades, patients with diabetic renal disease, have comprised a steadily increasing segment of the population with end-stage renal disease (ESRD).[95] In diabetes mellitus type I, increased capillary pressure and permeability are believed to play an important role in the pathogenesis of

diabetic microangiopathy.[96] Several authors have pointed out that in various organs, including the kidney, blood flow is increased.[96,97] In early diabetes, this leads to renal hypertrophy with enlargement of the glomeruli, both generally and in the amount of basement membrane substance. Later on, the kidneys of a diabetic are at risk from a specific lesion typified by the nodular glomerulosclerosis, the Kimmelstiel-Wilson-lesion. In patients with type I diabetes and micro-albuminuria, advanced structural changes in the glomerular basement membrane are seen.[98] Typically ESRD occurs in type I diabetes some 15-30 years after diagnosis of diabetes, usually within 2-3 years of onset of the nephrotic syndrome.[99]

Not very long ago, type II diabetes mellitus was believed to be a benign condition, especially in elderly patients, with respect to life expectancy and renal function.[100]

Now it is accepted that the rate of renal disease is equivalent in non-insulin-dependent diabetes mellitus (NIDDM) and insulin-dependent diabetes mellitus (IDDM).[101-104] Nowadays, because of the greater prevalence of diabetes type II, patients with NIDDM account for most of the diabetics on dialysis.[105,106]

A number of patients with type II diabetes have the classic Kimmelstiel-Wilson lesions in their kidneys. Others, however, have non-specific vascular and interstitial lesions with few glomerular changes or none at all.[107] A kidney afflicted with glomerulosclerosis may be more susceptible to diminished mesangial clearance function or immunologically mediated damage. Membranous and IgA nephropathies, focal segmental glomerulosclerosis and mesangiocapillary and extracapillary glomerulonephritis have been described in association with diabetes.[108] Biopsy studies carried out in subjects with proteinuria, but with a glomerular filtration fraction in the normal range have found low prevalences (between 10 and 20%) of glomerulonephritis.[109,110]

Improved glycemic control is known to slow the onset and progression of microvascular complications, but its effect on atherosclerotic disease has not been conclusively demonstrated.[111]

Nephropathy in NIDDM is strongly determined by genetics.[106,112,113] In clinical practice, the finding of a positive family history of cardiovascular events is a simple but powerful indicator for renal risk in NIDDM patients.

Non-insulin-dependent diabetics who develop nephropathy do so usually within 5-10 years of the diagnosis of diabetes, and the older the diabetic is at onset of nephropathy, the more rapid is the progression to ESRD.[114]

1.6.2. Hypertension

In the Baltimore longitudinal study of aging, a statistically significant correlation was found between mean blood pressure and the increase in serum creatinine in 1000 male volunteers between the ages of 22 and 97.[115] The overall conclusion was that the decline in renal function was independently correlated with age and mean arterial blood pressure, and that these variables were independent of each other. Thus, hypertensive patients without clinically detectable renal disease will have a greater expected decline in renal function than normotensive subjects.[116] Higher levels of both diastolic and systolic blood

pressure increase progressively cardiovascular morbidity and mortality.[117,118] Systolic blood pressure however, is a more powerful risk factor for cardiovascular diseases than diastolic bloodpressure in elderly. The Multiple Risk Factor Intervention trial showed that a systolic blood pressure of 160 mmHg was more closely associated with mortality than a diastolic blood pressure of 95 mmHg.[119] In the SHEP study the percentage of elderly (older than 60 years) with isolated hypertension was found to be over 10%.[120]
Untreated primary hypertension is very likely to cause renal damage.[121] The aging kidney's diminished functional reserve place it at risk for the progression of hypertensive arteriolar nephrosclersosis and also predispose to vulnerability related to reductions in blood flow and tissue oxygenation associated with transient decreases in intravascular volume and blood pressure.[122]
Many authors consider the prognosis of treated essential hypertension to be very good. They estimate that a small percentage (<2%) will develop chronic renal failure.[123,124] Others, however, do not share this optimism.
They point out that in the United States, one in 13 persons (7.7%) with hypertension will develop hypercreatinemia, and 4%-16% of treated hypertensive patients have proteinuria.[125,126] Several authors report a progression in the decline of the renal function.[78,127,128]

1.6.3. Other risk factors

Hyperlipidemia and race are other risk factors for declining renal function over time.[129] McCord first reported that hypertensive black patients were more likely to acquire renal failure due to nephrosclerosis than Caucasian patients.[130] Later studies confirmed this finding.[131-135]
While hypertension has a greater prevalence in black patients than in white patients, this difference alone cannot account for the increased incidence of ESRD in Afro-Americans.[136]
Lipid abnormalities are major contributors to cardiovascular disease (CVD) in elderly.[137] This is especially true in elderly diabetics.[138]
Patients with hypertension and glucose intolerance have lower GFR's than other persons of the same age. Glucose intolerance in combination with hyperuricemia, results in even lower GFRs.[139] In hypertensive patients with nephrosclerosis and normal fasting glucose, an oral glucose tolerance test revealed a type II diabetes mellitus in 52%.[140]
In women, there is an increase in prevalence of hypertension postmenopausal.[141] Estradiol decreases vasoconstriction and mediates vasorelaxation by stimulating vascular production of vasodilators as nitric oxide and prostaglandins.[142] In elderly women the reduction of estradiol production in combination with a diminished expression of vascular estradiol receptors increase the risk of hypertension.[122]

2. Renal disease in the elderly

2.1. Acute renal failure

2.1.1. Introduction

Elderly patients are at greater risk of developing acute renal failure (ARF) than younger patients due to their diminished renal reserve capacity.
The ability of the kidneys to withstand acute insults to renal function is compromised. The percentage of patients with ARF who require dialysis ranges from 20%-60%.[143,144]
It is useful to categorize ARF according to prerenal, renal and postrenal causes.[145] In Table 2.1, we categorize the main causes of ARF in elderly patients in this way. An increased incidence of ARF is demonstrated in the elderly, particularly in those receiving aminoglycoside antibiotics or after cardiovascular surgery. In a comparative study of 218 elderly patients (>60 years) and 816 younger patients (<60 years), Glickman et al. found ARF as the second most common clinical diagnosis, occurring three times as often in the elderly patients (14.2% vs. 3.9%).[146] This may be related to a higher incidence of multiple organ failure in the elderly as well as to the progressive renal impairment seen with normal aging.[147-149] A depression of the antioxidant system is present in critical ill patients with multiple organ failure (MOF). In patients with MOF and associated ARF this depression is even more pronounced, suggesting an additional effect on the antioxidative potential due to renal dysfunction.[150] Prognosis and survival are mainly related to comorbidity rather than to age.[151-154] Acute renal failure secondary to sepsis is associated with a very high mortality - up to 90%.[121] Elderly patients who survive ARF need more time to recover and often do not regain full renal function.[155]

2.1.2. Prerenal renal failure

Prerenal azotemia is the most common cause of ARF in the elderly.[156] Elderly patients are highly susceptible to ARF due to their predisposition to volume depletion as a result of their reduced capability to conserve sodium. An age-related decline in renal function and the high prevalence of atherosclerosis with consequences for renal blood flow are contributing factors.[157] Vomiting, diarrhoea, gastro-intestinal blood loss, the use of diuretics, often in combination with poor fluid intake, and congestive heart failure are all very common contributing factors in the elderly population.

Table 2A.1 Causes of acute renal failure in elderly patients

Prerenal causes	
Volume depletion	Blood loss Gastrointestinal loss, vomiting, diarrhoea Diuretics, glycosuria, NSAIDs, ACE-inhibitors
Decreased effective arterial volume	Decreased cardiac output, congestive heart failure, Myocardial infarction, cardiac arrhythmia Hepatic disease: cirrhosis Hypoalbumenia: nephrotic syndrome Sepsis
Renal Causes	
Glomerular	Acute glomerulonephritis Vasculitis
Tubular	
- Tubular necrosis	Ischemic (shock, sepsis) Toxic e.g. aminoglycosides, radiocontrast agents, amphotericin B
- Tubulo-interstial nephritis	Infectious NSAIDs, penicillin, thiazides sulpha compounds
- Obstruction	Myoglobulin, hemoglobin, Bence-Jones proteinuria, urate.
Vascular	Vasculitis, auto-immune diseases Malignant hypertension
Postrenal causes	
Upper tract	Stones Malignancy Papillary necrosis
Lower tract	Benign prostate hypertrophy Prostate, bladder, or pelvic carcinoma Strictures, valves

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) is of special interest in the aged. First of all, gastroduodenal damage is seen in 20%-40% of people who take these drugs, with high risks of peptic ulcers, and this may result in bleeding and even death.[158] Secondly, the risk of NSAID-related nephrotoxicity increases with age.[159] In situations where systemic circulation and/or renal perfusion is compromised, prostaglandin synthesis is increased, leading to vasodilatation, necessary to minimize renal ischemia. The use of NSAIDs under these conditions blocks vasodilatation with an inhibiting effect on renal blood flow and the risk of developing renal failure.[160]
The use of angiotensin-converting enzyme (ACE) inhibitors can also be associated with hemodynamically mediated ARF. Again, a state of reduced renal blood flow due to low intake or excessive diuresis forms the major risk factor for this complication. This complication can occur not only in patients with bilateral

renal artery stenosis, but also in patients with atherosclerosis of the smaller vessels of the kidney.[161,162]

2.1.3. Parenchymal renal failure

Acute tubular necrosis is the result of ischemic or toxic injury. Any prolonged cause of prerenal failure can evolve into acute tubular necrosis. Second to ischaemia, toxins are the most common cause of ARF. Drugs can damage the kidney by several mechanisms.
Damage resulting from decreased renal perfusion brought on by, for example, the use of NSAIDs and ACE inhibitors has already been mentioned. Direct toxicity to the tubuli has been described for aminoglycosides, radiocontrast agents, cyclosporine, cisplatin, tacrolimus, amphotericin B, methotrexate, foscarnet, pentamidine, and heavy metals. Cocaine, ethanol, and lovastatin can induce rhabdomyolysis resulting in damage to the tubuli. Intratubular obstruction can be the result of the use of sulphonamides, ethylene glycol (formation of calcium oxalate crystals), and chemotherapeutics (formation of uric acid crystals as a result of tumor lysis). Allergic interstitial nephritis has been described as a side effect of a number of drugs such as penicillins, cephalosporins, sulfonamides, rifampicin, NSAIDs, furosemide, thiazide diuretics, cimetidine, phenytoin, and allopurinol. A number of drugs (cyclosporine, tacrolimus, mitomycin, quinine, and conjugated estrogens) can also induce a hemolytic-uremic syndrome [163]

2.1.4. Postrenal renal failure

Obstruction of the urinary outflow tract can lead to ARF. It is important to detect such an obstruction in an early stage because removing of the obstruction increases the chance of recovery of renal function. Benign prostatic hypertrophy, carcinoma of the prostate, bladder, cervix, uterus, or rectum, or retroperitoneal malignancies are all important causes of postrenal obstruction, frequently seen in elderly patients. Ureteral stenting or percutaneous nephrostomy are possible options for removing the obstruction.

2.2. Chronic renal failure

Chronic renal failure is almost by definition a disease of the elderly. Reliable data on the incidence of chronic renal failure first became available when elderly patients were placed on renal replacement therapy (RRT). Glickman et al. report a rapidly increasing number of kidney biopsies in elderly patients after 1981.[146] This coincides with the gradual acceptance of elderly patients for RRT. However, many reports on renal failure in elderly patients mention only a clinical diagnosis.
When discussing renal biopsies in these patients, only the primary renal diagnosis is mentioned; secondary causes of renal insufficiency are excluded.[164] Secondary renal diseases caused, for example, by diabetes mellitus and hypertension, are likely to predominate in elderly patients. In the earlier mentioned study of Glickman et al. the most common clinical diagnosis

nephrotic syndrome/proteinuria was equally distributed over young and elderly patients (31.4% versus 32.1% respectively).[146] End-stage renal disease also occurred with almost equal frequencies in the two groups. Rapidly progressive glomerulonephritis was found to have a three times higher frequency in the elderly patient population. Thus it constitutes the third most common diagnosis in the elderly, whereas it is the ninth most common diagnosis in the younger age group. Diabetes and acute glomerulonephritis were equally distributed in both groups.

2.2.1. Morphological diagnoses

Nephrosclerosis is the most found morphological diagnosis in both elderly and younger patients.[117] In the Glickman et al. study, membranous glomerulonephritis and crescentic glomerulonephritis were both more common in elderly patients.[117] The frequency of diabetic nephropathy, chronic glomerulonephritis, acute glomerulonephritis, focal glomerular obsolescence, and tubular atrophy was approximately the same in both groups. Acute tubular necrosis was found in about 1% of each group. Other observers report a higher prevalence of nephrosclerosis, diabetes mellitus, obstructive uropathy, multiple myeloma, and amyloidosis in the elderly.[165-168]

The fact that renal disease in elderly patients has often more than one cause resulted in the diagnostic category labelled 'unknown'. Another reason for this high percentage may be the persistent reluctance to perform renal biopsies in elderly patients. A recent Dutch retrospective study of 122 elderly patients found the following primary diagnoses: tubulo-interstitial nephritis (13%), glomerulonephritis (8%), renal vascular disease (7%), diabetes mellitus (7%), and polycystic kidney disease (3%). In no less than 64 patients (53%) was the primary diagnosis unknown.[169]

A number of studies from different parts of the world report the cause of renal disease to be unknown at a rate varying from 10% to 24% (mean 24%).[170-175]

In the 1118 patients older than 65 years of age who entered RRT in the period from 1990 to 1992 in the Netherlands, diabetes mellitus (types I and II), glomerulonephritis, renal vascular causes, and polycystic kidney disease comprised 55% of the primary diagnoses. In 142 patients (13%) the diagnosis was unknown[176] (Table 2A.2).

In the period from 1984 to 1992, the distribution over the listed diagnoses remained fairly constant with one exception: renal vascular disease. (Table 2A.2) This is most likely the result of the decreasing mortality secondary to acute cardiovascular disease.[146] The number of patients who survive an acute cardiovascular event is still increasing.

This development, resulting in a longer life expectancy may be the cause of a higher percentage of subsequent complications of atherosclerosis such as renal insufficiency. Some authors also suggest a negative influence of our modern industrialized society on renal function resulting in a rising incidence of renal failure.[177]

Table 2A.2 Clinical diagnoses in patients 65 years of age and older on renal replacement therapy

	1984-1986		1987-1989		1990-1992	
Diabetes type I	27	(5%)	49	(6%)	72	(6%)
Diabetes type II	28	(4%)	43	(5%)	62	(6%)
Glomerulonephritis	70	(14%)	78	(10%)	103	(10%)
Pyelonephritis	78	(15%)	94	(12%)	111	(10%)
Renal vascular disease	121	(24%)	207	(25%)	349	(31%)
Polycystic kidney disease	17	(3%)	32	(4%)	39	(3%)
Other	99	(19%)	181	(22%)	248	(21%)
Unknown	84	(16%)	131	(16%)	142	(13%)
Total	514	(100%)	815	(110%)	1118	(100%)

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Chapter 2B

Renal replacement therapy in the elderly

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Abstract

In all industrialized countries, life expectancy has risen in the past 100 years. The number of elderly patients reaching end-stage renal disease (ESRD) and requiring renal replacement therapy has also increased. During the past few decades, the pattern of ESRD has changed significantly with the emerging predominance of elderly patients. The causes of this phenomenon are manifold and include an increasing number of chronic diseases typical of the 'third age', such as type 2 diabetes and vascular disease. In many species, a consequence of aging includes deterioration of renal function, partly due to structural alterations, and partly as the result of a diminishing blood flow. In humans, the aging kidney is characterized by modifications resulting from organic and functional disturbances. In particular, type 2 diabetes mellitus has emerged as an important condition, the microvascular and macrovascular complications of which are a common cause of morbidity and mortality in older patients. In part II of this review, the specific aspects of renal replacement therapy in the elderly will be discussed.

1. Introduction

In almost all developed countries of the world, the elderly represent an increasing percentage of the patients in renal replacement therapy (RRT) programs. In 1967, only 7% of the chronic dialysis population in the United States was 55 years or older.[1] In 1985, almost 60% of all new entrants in dialysis programs had a mean age of 55.5 years.[2] In 1995 the median age of the patients who enrolled the the Medicare ESRD program was 64 years at start of the renal replacement therapy.[3] In 1997, in the US, over 300,000 patients were receiving RRT; 194 720 of them were aged 65 or over, comprising over 34% of the prevalent end-stage renal disease (ESRD) population. In the same year over 79 000 patients were started on ESRD treatment. Patients aged 65-74 years had the highest recorded incidence rate; they were closely followed by those of 75 years of age and over.[4] The United States Renal Data System (USRDS) also indicates a yearly rise in the incidence of treatment of elderly patients (Table 2B.1).

Table 2B.1 Treated Medicare ESRD Incidence Counts[4]

Age	Count	% of Total	Rate per Million
0-19	1,069	1.4	13
20-44	11,800	14.9	109
45-64	26,253	33.2	545
65-74	22,056	27.9	1296
75+	17,924	22.7	1292
Total	79,102	100	287

The same trend towards an increasing number of elderly patients in RRT programs starting the late 1970s and 1980s, can be seen in Canada, Europe, Australia, and Japan.[5-9] In the United Kingdom this trend was initially less steep due to the the country's budget restrictions for health care.[10,11]
Among all new patients starting renal-replacement therapy in England and Wales, the percentage of patients who were over 65 years increased from 11% in 1982-84 to 39% in 1995.[12]
What we see is not only that more elderly patients admitted to RRT programs, but also the age at which they were accepted gradually rose. During the 1980s, patients 75 years of age and older first enrolled RRT programs.[13] Nowadays this age group showes almost the highest incidence among patients starting renal replacement therapy.[4] In 1990, a questionnaire on the subject of treatment for elderly patients was sent to French nephrologists. The results showed that for patients younger than 90 years, age was no longer considered a good criterion for excluding patients from dialysis.[14] Arguments for rationing dialysis by age,

like poor survival expectancy, less quality of life and lower social obligations of elderly patients, and of course the high costs of renal replacement therapy, have been debated, leading gradually to the acceptance that age should not be a contraindication for RRT.[15-17]

2. Patient selection

After disregarding chronological age as an exclusion criterion, the concept of biological age is sometimes used.[18] However, such a judgment tends to be subjective, if not arbitrary. Nevertheless, selection does take place.[19,20] A Swedish study reported that only 40% of all patients over 70 years of age with renal failure actually received treatment.[21] A British survey reported that only 3 out of 37 patients aged 70-100 with end-stage renal failure underwent RRT.[22] A survey of physicians in the United Kingdom revealed that a previously healthy octogenerian would not referred for dialysis by 68% of primary care physicians, or accepted for renal replacement therapy by 28% of nephrologists.[23] A reluctance of family practioners to refer elderly patients for renal replacement therapy has been mentioned earlier.[24]

Yet, in the literature not very much evidence-based criteria can be found on which patient selection for RRT should be based. Severe dementia is a selection criterion commonly mentioned. Self-determination and autonomy are considered to be very important in this respect.[25] In the above mentioned survey of French Nephrologists, 90% refused patients 75 years of age and older if they were not independent and did not have a supportive family.[14] If the patient is truly competent, then he or she should have the right to make a decision based on informed consent.[26] However, decision making in this field is not always considered to be easy.[27]

In the United Kingdom criteria were published for the acceptance of patients on (local) renal replacement therapy programs.[28] These criteria were based on potential life years to be gained from treatment, absence of significant comorbidity, and the capability of independent living. These recommandations showed to be a reasonable starting point following the results of a British hospital based cohort study.[29] Over a four year period 292 patients with a mean age of 61.3 years starting planned or unplanned dialysis were defined on basis of age, comorbidity and functional status. Age, comorbidity and functional status were predictors of survival and morbidity. Age was heavily outweighed by the severity of comorbidity in predicting survival. The number of comorbid systems did not discriminate as well as the comorbidity severity score. Functional status (defined as the Karnovsky score) at the time of presentation, three months before presentation and the change in between all were usefull in predicting survival. The authors suggest that the question " how was the patient a few weeks ago before he or she became very unwell?" may be usefull in the treatment decision. The limited significance of age and the importance of comorbidity status was also found in the North Thames prospective cohort study.[30] In this study a follow-up was made of 221 patients, aged 70 years and older, with end-stage renal disease. Mortality was significantly associated with age 80 years and older and

peripheral vascular disease, but not with diabetes mellitus, ischemic heart disease, cerebrovascular disease, chronic obstructive airway disease, sex or treatment modality.
All these results clearly indicate that age alone should not be used as selection criterion for renal replacement therapy. However, the burden that renal disease and dialysis therapy imposes on elderly patients should not be underestimated. In the United States, probably the highest percentage of elderly patients are accepted for RRT. This lenient policy creates another problem: withdrawal from dialysis. Approximately one out of every five dialysis patients withdraws from dialysis before death.[31] This does not include patients who have stopped dialysis because of restored of renal function. Patients are more likely to withdraw from dialysis if they are white, female, diabetic, older than 65 years, or living in nursing homes.[32,33] Almost a quarter of all deaths in dialysis patients 65 years and older were preceded by withdrawal from dialysis in the period 1994-1996.[34]
Accordingly, the decision to initiate renal replacement therapy in an elderly patient should be made after due consideration of the individual patients physical and medical status as well as his or hers psychlogical well-being.

3. Treatment modalities

3.1. Hemodialysis

The most common treatment modality in elderly patients is hemodialysis (HD). In the United States, around 80% of the ESRD patients aged 65 years and over are treated with hemodialysis and only about 10% - 12% of the patients 75 years and older are treated with peritoneal dialysis (PD).[35,36] In Europe this percentage is similar, with the exception of the United Kingdom. Only in Australia and New Zealand is the distribution between HD and PD in elderly patients almost 50/50.[37,38]
In the recent past, many technical improvements have been made in HD, such as the use of bicarbonate dialysate, varying the sodium content of the dialysis fluids, and better methods to assess fluid status in patients on hemodialysis.[39-41] The introduction of re-combinant erythropoietin has also offered great advantages, despite the risks of hypertension and ischemic complications.
Elderly patients can do very well on HD. As early as 1979 Chester et al. reported a 2-year survival rate of 42% for 45 HD patients older than 70 years.[42] Age did not correlate with survival in this survey, nine patients older than 80 years had even a survival of 41%. Although elderly dialysis patients are thought to have a lower mortality risk than younger dialysis patients, Mignon et al. report a threefold mortality risk for 75-year-old dialysis patients compared with an age-matched cohort of non-dialysis patients.[43]
The EDTA-ERA Registry reports a 5-year survival rate of 40% for patients from 65 - 69 years of age; for patients 70-74 years of age it is nearly 30%; for those over 75 years it is over 20%. Ten-year survival is slightly over 20% in the age group 60 - 64 and less than 10% in the group over 75 years.[44] Survival rates

differ in the different European countries. In Spain, Portugal, and Italy, the survival rate is much higher than in Austria, Norway, and Sweden.[45] An important reason for this difference is probably the mortality from myocardial infarction and cardiac ischemia.[46,47] It may also partly attributed to the higher incidence of diabetes mellitus in the northern European countries. However, two recent British studies showed no significant influence on mortality of diabetes and ischemic heart disease.[29, 30] Severe comorbidity influenced mortality more than the number of comorbidities. Functional status at the start of the dialysis is also important in assessment of survival.
Numerous studies show that mortality of HD patients is related to the length and frequency of dialysis treatment. Higher mortality is observed in patients treated with fewer hours of dialysis.[48,49]

3.1.2. Complications

There are a number of complications of HD in elderly patients. First of all, some authors mention hypotension as a complication more frequently seen in elderly patients than in younger dialysis patients.[50,51] However, this difference is not found in all series.[52] A substantial proportion of HD patients (32% - 62%) shows a decreased left ventricular (LV) ejection fraction due to LV hypertrophy.[53,54] This may markedly affect myocardial oxygen consumption, especially in patients with pre-existent cardiac disease, resulting in congestive heart failure.[55-57] Another consequence of hypertrophy and a decrease in LV compliance is an increased incidence of arrhythmia's and sudden death.[58] Malnutrition is frequently seen in elderly patients on maintenance HD.[59] Several studies suggest that malnutrition is an important risk factor for morbidity and mortality in HD patients.[60,61] Especially the presence of low serum albumin, low prealbumin, low serum cholesterol and other markers of nutritional status are correlated with increased mortality in dialysis patients.[62-66] Treating malnutrition leads to better results when a concomitant anemia is also treated.[67]
Complications of the vascular access are responsible for a substantial percentage of the hospital admissions of the elderly ESRD patients. Ifudu et al found that diabetes mellitus and age were no independent risk factors for vascular access hospitalisation but were associated with prolonged hospital stays.[68]
Hemodialysis patients have a greater cardiovascular mortality than non-uremic patients. They have a higher prevalence of complicated atheromatous laesions.[69] Calcification of these lesion is probably associated with secondary hyperparathyroidism resulting in an increased calcium-phosphate product.[70] In favour for this hypothesis is the finding that progression of atherosclerosis is significantly lower in hemodialysis patients with parathyroidectomy than in patients without.[71]
Finally prognosis of patients on HD is linked to renal vascular disease and, of course diabetes mellitus.[61,72]

3.2. Peritoneal dialysis

Peritoneal dialysis (PD) offers some important advantages to elderly patients, especially a better maintenance of fluid balance, preservation of residual renal function, and the fact that there is no need for vascular access.[73,74]

Numerous authors consider PD the treatment of choice for the elderly, particularly for those with hemodynamic instability or cardiovascular disease.[75-78] However, for patients with sensorial impairment, such as reduced vision, motor handicaps, or impaired capabilities in learning the technique, PD is not a suitable modality unless there is adequate family and/or social support.[79,80]
Complications of PD are catheter-related or infectious (peritonitis). The incidence of these complications is not higher in elderly patients than in young patients on PD.[81,82]
A large survey reported that after 1 year of PD 60% of patients younger than 60 years were free of peritonitis vs. 65% of patients elder than 60 years. At 3 years these figures were 38 and 46% respectively. At 7 years 30 and 38%.[83]
Relapsing peritonitis is a feature in 8 to 16% of patients with peritonitis, whilst catheter removal is necessary in up to 15% of the patients, mortality due to peritonitis is 1 to 3%.[83,94] Death is the result either from sepsis or related complications, especially when the causing micro-organism is Gram-negative or fungus.[85,86]
The causes of peritonitis are similar in young and elderly patients on PD.[87] Inguinal or abdominal hernias, fluid leakage, and vascular ischaemia of the lower extremities have a higher incidence in older PD patients than in younger patients.[88]
In terms of mortality, no major differences have been found between HD and PD.[89] Vascular renal disease, advanced age, co-morbidity, and diabetes mellitus are major determinants of mortality.

3.3. Renal transplantation

In Europe, the proportion of elderly patients (60 years and older) treated by renal transplantation has increased from 2.9% in 1983 to 9.9% in 1992.[90] In the United States of America in 1997, 36% of all kidney transplants were performed in patients 50 years or older, and 5.7% were in patients age 65 years or older.[91]
Age has long been considered a risk factor for renal transplantation. Older patients have been found to have more (and more serious) complications and a higher mortality.[92,93] This increased risk was associated with transplant surgery and immunosuppressive treatment.[94,95] Graft survival in younger patients has been better than in older patients, primarily because of graft loss secondary to the elderly patient's death.[96-102] On the other hand, graft loss due to rejection is less common in the elderly.[98, 100,103]
The addition of cyclosporine A to the immunosupportive regimen has given a significant improvement in the survival of elderly patients receiving cadaveric renal transplants.[104] Monotherapy with cyclosporine in patients over 55 years of age was reported to give a graft survival of 93 % at 1 year and 90% at 3 years

with patient survival of respectively 96 and 94% despite a high incidence of acute rejection.[105]
The Spanish Monotherapy Study showed similarly good survival figures on monotherapy cyclosporine in elderly patients.[106] These studies made it clear that immunosuppressive regimens without corticosteroids may be desirable in elderly patients.
Experiences of double therapy suggest that early withdrawal of corticosteroids is favourable in older recipients of kidney transplantation.[107-109] Triple therapy using corticosteroids, azathioprine, and cyclosporine or antithymocyte globulin (ATG), corticosteroids, and cyclosporine have also led to good results in elderly patients.[101,110,111] The main problem with this kind of regimens is the increased incidence of infections, especially cytomegalovirus infections, and the fact that elderly patients as less able to cope with infections than younger patients.
In general can be said that renal transplantation results in elderly recipients have improved since the introduction of cyclosporine. Mortality, however, remains high, mainly following cardiovascular diseases and infections. In principle all immunosuppressive drugs can be used in elderly patients, but corticosteroids should be used with extreme caution. Older patients should be treated with lower doses and less immunosuppressive drugs than young patients to avoid overimmunosuppression with infectious complications.[112]
Doyle et al. reviewed the course of 206 consecutive primary renal allograft recipients, aged 60 years or older between 1980 and 1997, to identify risk factors that predicted a poor outcome.[113] Risk factors for graft loss were; current tobacco use (RR 8.1), pre-transplant non-skin malignancy (RR 3.9), Donor age >50 years (RR 2.3), pre-transplant vascular disease (arterial peripheral disease or venous thrombosis) (RR 2.1), time on the waiting list <1 year (RR 1.8), and age 65 to 70 (vs. 60-64) years (RR 1.7). Mortality was determined by pre-transplant non-skin malignancy (RR 5.0), pre-transplant vascular disease (arterial peripheral disease or venous thrombosis) (RR 2.2), Age >70 years (vs. 60 to 64) (RR 2.7), Donor age >50 years (RR 1.9), and current tobacco use (RR 7.9).
The authors postulate that screening for these risk factors will enable a selection of a group of low-risk elderly patients with good graft and survival outcomes.
Patients with diabetes mellitus type II are considered as a high-risk group. Not only are they generally over 50 years of age, but also they have considerable comorbidity. A recent survey showed that type II diabetics have a less overall graft survival in comparison with type I diabetics and non-diabetics over 50 years of age.[114] The most common cause of graft loss is death with function. As far as immunologic graft loss is concerned no difference between the three groups could be found.
Thus, in elderly transplantation recipients, there is higher rate of graft loss due to an age-related increased mortality. This, however, is balanced by a significant lower number of graft losses from immunologic problems (acute and chronic rejection). Renal transplantation therefore, can offer a substantial survival advantage over dialysis in careful selected group of elderly ESRD patients.[115,116]

4. Conclusions

The incidence of ESRD is increasing in elderly patients. This is due to an ever-increasing life expectancy, better survival after acute manifestations of cardiovascular disease, and an age-related decrease in renal function. A large percentage of the patients in chronic renal replacement programs is above the age of 65.
The percentage of these patients who are accepted for renal transplantation is still low in comparison to patients in lower age categories, resulting in an increasingly older population using dialysis facilities.
Consequently, dialysis is not as readily available as it was in the past. Selection for RRT does occur. Yet, it is not clear which parameters can be employed to predict treatment outcome. It will become increasingly important to determine not only which patients should be treated with RRT but also for which patients this therapy is *not* indicated. Both measures will help prevent much unnecessary suffering and medical interventions for these patients.

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Chapter 3

Clinical characteristics of elderly patients with end-stage renal disease: a retrospective study in the Dutch population

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Abstract

Objective

A retrospective study was carried out among 331 elderly patients (65-95 years of age) in four hospitals with dialysis facilities in order to assess the incidence of end-stage renal disease (ESRD) as well as the accessibility of renal function replacement programs for the elderly.

Results

The incidence of ESRD was estimated to be 2.2 per 1000 elderly inhabitants. There were more men than women (59/41%) in this group. Patients had an extensive medical history and comorbidity. The mean number and the diversity of events in the medical history were high (4.5 in male and 5.3 in female patients). Cardiovascular disease, hypertension, gastro-intestinal disorders, and diseases of the urogenital tract accounted for 63% of these events. We also found extensive comorbidity with a Charlson index of 1 in 29.9% of the patients and of 2 or more in 16% of these patients. While few patients had renal biopsies taken, a large number of diagnoses related to ESRD were made. In 118 patients the onset of renal failure was acute. The clinical diagnoses related to ESRD were multiple (580 diagnoses in 331 patients). Hypertension, renal vascular disease, postrenal causes, cardiac failure, and diabetes mellitus were the most frequently occurring diagnoses related to ESRD.

There were135 patients (41%) in a renal function replacement program. Seventy (52%) of the patients treated did not survive the 2-year inclusion period; 112 (57%) of those not treated by renal replacement therapy (RRT) died within the same 2 years. In both groups, comorbidity and age played an important role.

Conclusions

The incidence of renal failure in our elderly population was higher than that reported in the literature. This is due to the fact that our method of data collecting differs from most surveys. Accessibility of RRT programs for elderly patients in our region is limited and age is a major criterion. However, the survival rate - 51% for treated versus 57% for untreated patients - indicates that patient selection for RRT is not optimal.

Introduction

Prior to 1980, few elderly patients with end-stage renal disease (ESRD) were able to participate in dialysis programs. Since then, however, the situation has gradually changed.

Patients 65 years of age and older now represent the most rapidly growing segment of the ESRD- population in North America, Europe, and Australia.[1-5] A number of factors are responsible for this increase.

First of all, technical improvements in the field of vascular access, in dialysis procedures, and in membrane materials and dialysate fluid composition, as well as the increased availability of dialysis facilities, have made it possible to treat a growing number of elderly patients. Renal transplantation, while fairly successful in carefully selected elderly patients, is still largely confined to younger patients due to the scarcity of transplant organs.[6-8] Therefore, once elderly patients are admitted to chronic renal replacement programs, they usually remain in dialysis, leading to an increase in the mean age of patients undergoing renal replacement therapy (RRT). There has also been a substantial increase in the number of patients with diabetes mellitus in the ESRD and dialysis populations during the past two decades. This is due both to an increased prevalence of diabetes in the general population and to an increased acceptance of diabetics into renal replacement programs.[9,10] In the 1960s and early 1970s the survival of diabetics in renal function replacement programs was reported to be 3-6 months; this was because of high morbidity and mortality rates attributed to blindness and coronary artery, cerebrovascular, and peripheral vascular diseases.[11-14] Thus, during that period, in North America and Europe, diabetes was considered to be an exclusion criterion for dialysis. Since the late 1970s and early 1980s, better results have been reported, and today diabetics are frequently seen undergoing dialysis.[15,16]

Most reports on ESRD in the elderly focus on patients enrolled in renal function replacement programs. Despite the fact that many elderly patients, when carefully managed, can adjust well to ESRD, a substantial number of them are not seen in the dialysis department.

In a survey of physicians in the United Kingdom, a previously healthy octogenarian would not be referred for dialysis by 68% of primary care physicians or accepted for dialysis by 28% of nephrologists.[17]

The present study was undertaken to assess the incidence of ESRD in elderly patients in a well-defined region, as well as to gain insight into the clinical presentation and characteristics of these patients. We were also interested in determining the accessibility of RRT programs for these patients.

Subjects and methods

We retrospectively studied the incidence of ESRD, the clinical data of patients with ESRD, the number of patients admitted to RRT programs, and the survival of ESRD patients with and without RRT. To this end, a search was performed of the laboratory records in the four hospitals with dialysis facilities in our region - Laurentius Hospital Roermond, Maasland Hospital Sittard, Atrium Hospital Heerlen, and the University Hospital in Maastricht - of patients 65 years and over with a serum creatinine of at least 400 μmol/l (4.5 mg/dl) measured between January 1, 1992 and December 31, 1993 the inclusion period.
These four participating hospitals are situated in the region of South Limburg, the Netherlands. This region has a total population of 1.25 million inhabitants and shares borders with Belgium to the south and the west and with Germany to the east. Insurance policies do not allow medical treatment of patients across the border. Therefore, in every respect, this region is well defined.
The four hospitals have a target population of about 1 million people. All laboratory data were retrieved from computerized files of the hospital information systems. The laboratories of these hospitals perform tests on in-hospital patients and on those attending outpatient clinics, as well as for all primary care physicians in this region.
The medical files of these patients were studied and data were extracted concerning age, gender, socioeconomic status, functional status, medical history, primary renal diagnosis, comorbidity, medical interventions, and clinical course. Comorbidity was defined as diseases present at the moment the diagnosis ESRD was made. Medical history and comorbidity were entered following the International Classification of Diseases, 9th revision, Clinical modification (ICD-9-CM).[18] We estimated the severity of comorbidity using the Charlson index.[19] This index contains a list of nineteen conditions, some of them representing two degrees of severity of the same condition. One of these conditions, moderate or severe renal disease, was not scored in our population since it was the primary disease.
The interval between the first indication of impaired renal function and the moment serum creatinine reached a value of 400 μmol/l or more was referred to as the renal history. A short renal history (<4 weeks) was defined as acute renal failure, a longer renal history as chronic renal failure.
In cases of RRT, we discriminated between acute therapy (started within 4 weeks after reaching a serum creatinine of 400 μmol/l or higher) and non- acute therapy (started after 4 weeks of the onset of ESRD).
All statistical analyses were done using SPSS for Windows 7.5 (SPPS Inc., Chicago). Data are presented as the mean value ± SD or number (percent). Student's *t* test was used to compare continuous variables. For categorical variables, the chi-square test or, when appropriate, the Fischer exact test was used. Survival was calculated from the moment the patient entered the study. Patients still alive at the end of the study (31-12-1999) were censored. The

survival curves were made using the Kaplan-Meier procedure, a method of estimating time-to-event models in the presence of censored cases.
The study was approved by the medical ethics board of the university hospital of the University of Maastricht.

Results

Patients

During the 2-year study period, 567 patients aged 65 years or older were found to have a serum creatinine of at least 400 μmol/l.
Data could be obtained for 331 of these patients - 194 men (59%) and 137 women (41%) - due in part to incomplete records and in part to the fact that the hospital's laboratory facilities are also open to general practitioners. Several patients of the primary care physicians were not referred to the hospital, and thus not registered in hospital records.
Our findings suggest a yearly presence of 280 elderly patients with ESRD in the region of our hospitals (target population 1 million). At present, 13% of the total population is 65 years of age or older, so we estimate the yearly prevalence of ESRD in the elderly population to be 2.2 per 1000 elderly inhabitants. The clinical characteristics of our 331 patients are summarized in Table 3.1.

Table 3.1 Basic clinical characteristics

	Male	Female
Number of patients	194	137
Median age	74 (65-92)	73 (65-95)
Mean age	74.18 (SD 6.51)	74.5 (SD 7.17)
Age groups		
64-70	62 (32%)	48 (35%)
71-75	54 (28%)	34 (25%)
75-80	49 (25%)	25 (18%)
>80	29 (15%)	30 (22%)
Serum creatinine	654 μmol/l (SD 271.64)	618 μmol/l (SD 254,09)
Body weight (mean)	72.5 kg. (SD 11.5)	62.5 kg (SD 12.8)
Height (mean)	172.1 cm. (SD 5.8)	163.7 cm (SD 6.2)
BMI	24.5 kg/m^2	24.4 kg/m^2
RR systolic	147.3 mmHg (SD 35.2)	150.2 mmHg (SD 36.7)
RR diastolic	80.8 mmHg (SD 17.6)	81.5 mmHg (SD 19.5)
Heart frequency	86.9 b/min (SD 19.4)	88.3 b/min (SD 18.6)
Irregular pulse	17	9
Pulmonary edema	49	28

There was no significant difference in age between the male and female patients. In almost every age group, there were more male than female patients. One-third of all patients were in the youngest age group (64-70 years) and 18% were in the oldest age group (>80 years).
The mean serum creatinine was 639 μmol/l (range: 400–1845 μmol/L; SD: 264.74); no statistical difference could be found between male and female patients (Table 3.1).
The mean body mass index (BMI) of the total group of patients was 24.4 kg/m^2. These data are comparable with those in the normal Dutch population.[20] However, the percentage of obese persons was lower in our group than in the general population (7.4% vs. 11.5%).
We estimated the renal function of these patients using the Cockcroft and Gault formula for age-adjusted creatinine clearance.[21] We found a mean creatinine clearance (Ccr) of 11,1 ml/min.
In male patients, the mean Ccr was 10 ml/min (range: 3–25 ml/min; SD: 3.59), and in females 8 ml/min (range: 2.21–16; SD: 2.98)
The mean systolic blood pressure was 148.5 mmHg at the moment of first admission. Female patients had a higher systolic blood pressure than male patients (150.2 vs. 147.3 mmHg), leading to an overall statistically significant difference between the groups ($p<0.05$). A total of 18 patients (9 male and 9 female) had a systolic blood pressure below 99 mmHg. A systolic pressure above 180 mmHg was found in 70 patients (36 male and 34 female).
The mean diastolic pressure was 80.8 mmHg in the male patients and 81.5 mmHg in the female patient group. The percentage of patients with a diastolic blood pressure of 95 mmHg or more was 14.4% in the male group and 15.8% in the female group.
The mean pulse frequency was almost the same in the two patient groups (87 b/min vs. 88 b/min for males and females, respectively). Clinical signs of supraventricular rhythm disorders were present in 17 male and 9 female patients.

Socio-economic status

185 patients were living with a partner at the moment they developed ESRD, significantly more male patients than female patients (Table 3.2). On the other hand more female patients were widowed. No statistical significant differences were found between having children or the number of children between male and female patients. The mean number of children was 2.3 for male patients and 2.5 for female patients. In 35% of the male patients and 39% of the female patients the children provided at least some care.
For almost 100 patients it was possible to retrieve information over the former profession from the medical file. This was the case in 84 male and 10 female patients. The former occupations were classified using the International Standard Classification of Occupations (ISCO-88). Table 3.2 shows the distribution over the ten major groups. Group 7 craft and related trade workers is most often found. In this group are 26 male patients who used to work in the coalmines that were in operation in this part of the Netherlands upon to 1969.

Table 3.2 Former profession

	Male patients		Female patients	
	N	%	N	%
Social status				
Living with partner	129	67	56	41
Widowed	40	21	60	44
Divorced	2	1	4	3
Not married	20	10	16	12
Unknown	3	1	1	1
Children				
No	44	23	40	29
Yes	136	70	91	66
Unknown	14	7	6	4
Care provided by children				
No	126	65	83	61
Yes	68	35	54	39

Table 3.3 Former occupation of 100 patients with ESRD classified according to the international standard classification of occupations

Former profession	Male patients	Female patients
1 Legislators, senior officials and managers	15	
2 Professionals	8	1
3 Technicians and associate professionals	9	2
4 Clerks	2	
5 Service workers and shop and market sales workers	1	
6 Skilled agriculture and fishery workers	2	2
7 Craft and related trades workers	44	3
8 Plant and machine operators and assemblers	3	1
9 Elementary occupations		
0 Armed forces		1
Total	84	10

Medical history

The medical history of the relatively aged study group was extensive, including a total of 1593 events. Only seven patients (one female and six male) did not have a single event in their medical history (Table 3.4).

Table 3.4 Number of events in medical history of 331 patients with ESRD

Events	Number of patients	Percentage
0	7	2.1
1-2	61	18.4
3-4	92	27.7
5-6	85	25.6
> 6	86	25.9
Total	331	100

In the remaining 136 female patients, a total of 723 events were reported, a mean of 5.3 events per patient. In the male group, medical history showed a total number of 870 events, or a mean of 4.5 events.
Cardiovascular disease, and especially ICD 401-403, ICD 410-414, and ICD 440-448, comprised about one-third of the medical events in the patients' history (36.3% in the male group and 30% in the female group). The number of patients who only had an event from this group is, however, limited. There were five patients with only coronary artery disease, four with only hypertension, and six with only arterial vascular disease in their medical history.
A combination of two cardiovascular diseases without another disease occurred in six patients; three manifestations of cardiovascular disease without an event from another group of diagnoses were seen in only five patients.
Besides cardiovascular diseases (ICD 390-459), Gastro-Intestinal diseases (ICD 520-579) and diseases of the urogenital tract (ICD 580-629) form the majority of diseases found in the medical history. These three groups accounted for 63% of the events among the male patients and for 55% of the events among the female patients.
When events from each diagnostic group were studied as dichotomous variables, some significant differences could be found between male and female patients. A higher incidence of endocrinological diseases and gastrointestinal diseases was found in the female patients. Chronic pulmonary diseases were more often seen in the group of male patients. The latter is probably due to the fact that many of our male patients used to work in coalmines that were once located in this region.

Comorbidity

Comorbidity was also extensive in our patients. Forty patients had no comorbidity at the moment of onset of renal failure (Table 3.5). In male as well as female patients, cardiac disease (mainly cardiac failure) was the most frequently occurring comorbidity. Other diseases frequently seen in both male and female patients were GI-tract diseases, urogenital tract diseases, and malignancies (Table 3.6). Type 2 diabetes mellitus was frequently seen in female

patients. Again, pulmonary diseases were frequently encountered as comorbidity in the male patient group. There were no significant differences in the total number of diseases between male and female patients.
A Charlson score of zero was found in 179 patients, 99 male and 80 female (Table 3.7).

Table 3.5 Number of comorbidities

No. Comorbidities	Number of Patients (%)	Male	Female
0	40 (12.1)	19	21
1	124 (37.5)	72	52
2	117 (35.3)	71	46
3	50 (15.1)	32	18
Total	331 (100)	194	137

Table 3.6 Total counts of comorbidity

	Total	Male pts	Female pts
Cardiac diseases	127	79	48
GI-tract diseases	61	39	22
UG-tract diseases	52	31	21
Malignancies	34	22	12
Arterial vascular disease	32	18	14
Pulmonary diseases	25	21	4
Hematological diseases	23	13	10
Endocrinological diseases	20	9	11
Other	44	26	18

Table 3.7 Charlson index

Charlson index Score	Total Patients (%)	Male (%)	Female (%)
0	179 (54.1)	99 (51.0)	80 (58.3)
1	99 (29.9)	62 (32.0)	37 (27.0)
≥2	53 (16.0)	33 (17.0)	20 (14.5)

Renal history

There was a wide range in renal history (Table 3.8). The median renal history in our group was 13 months (SD = 83 months). In 118 patients it was short: ESRD developed within 1 month, in 112 patients even within 2 weeks.
Thus, in about one-third of our population of elderly patients, we found an acute onset of renal failure. The percentage of patients with acute renal failure

increases with age. In patients aged 80 years and over, 46% had a short renal history.

Table 3.8 Renal history

Renal history	Male patients	Female patients	Total
≤ 2 weeks	65	47	112
≤ 1 year	22	17	39
≤ 5 years	43	35	78
> 5 years	51	35	86
Total	181	134	315

In contrast, a number of patients developed renal failure slowly, over a long period of time. In 86 patients, renal history was 5 years or more; in 44 of these patients, renal history even exceeded 10 years. The largest percentage of patients with a long renal history (32%) was found in the youngest age group (65-70 years). In 16 patients, renal history could not be computed due to missing data.

Renal diagnosis

In the records we studied, there was a total of 580 diagnoses related to ESRD, a mean number of 1.7 diagnoses in the male and 1.8 in the female patient group (Table 3.9).
This abundance of diagnoses is probably due to the fact that a renal biopsy was performed in only two patients in order to establish a pathological diagnosis of ESRD. Hypertension, vascular renal disease, postrenal causes, and cardiac failure were most frequently mentioned among the male patients. Taken together, these diseases comprised 50% of the causative diagnoses made in the group of male patients. In the female patient group, hypertension, type 2 diabetes mellitus, renal vascular disease, and cardiac failure were the most frequently reported causes of renal failure. These four diseases made up 50% of the diagnoses in the female patients. Hypertension, type 2 diabetes mellitus, and glomerulonephritis were reported significantly more often in female patients, whereas postrenal obstruction and unknown cause were significantly more often present in the male patient group. Dehydration was more often present in female patients, but the difference was not statistically significant.
In only 13 patients was a positive family history of renal disease mentioned. This is probably due to the fact that an inherited renal disease becomes manifest much earlier in life.

Table 3.9 Renal diagnosis

Diagnosis	Male patients	Female patients	
Hypertension	43	46	P=0.021
Vascular renal disease	50	25	
Diabetes mellitus	26	36	P=0.003
Postrenal cause	44	12	P=0.001
Cardiac failure	29	21	
Postoperative renal failure	24	10	
Dehydration	16	18	
Malignancy	20	13	
Nephrosclerosis	20	17	
Sepsis	10	13	
Glomerulonephritis	12	17	P=0.049
Nephrocalcinosis	9	12	
Other	5	5	
Unknown	21	6	P=0.035
Total	329	251	

Renal replacement therapy (RRT)

A total of 135 patients (41%) from our group of 331 elderly patients with ESRD were admitted to a renal function replacement program. In most cases, passive center hemodialysis was the choice of treatment; only 19 patients received peritoneal dialysis (CAPD).
Most patients treated were from the youngest age group. This group contained 39% of all male patients treated and 43% of all female patients treated. The percentage of patients treated declined with age: in the highest age group, only one out of every five patients was treated with RRT.
A different picture arises when we take into account the way RRT was started. Acute RRT was undertaken in 33% of the patients treated in the youngest age group. In the three older age categories, this percentage was 46%, 63%, and 75%, respectively.
A relation was found between the use of RRT and the primary renal diagnosis. In patients diagnosed as having nephrosclerosis, glomerulonephritis, or polycystic renal disease, RRT was more frequently applied. Postrenal causes of renal disease, and cardiac diseases provided less reason for starting RRT. Of course dehydration never was a reason for RRT.

Of the 135 patients treated, 62 (33 male and 29 female) died. Twenty-one patients did not survive 1 month on RRT. Another 11 patients died within 1 year after starting therapy. In the second year after starting RRT, 8 more patients died. All deaths within 2 years after starting therapy occurred in the group of patients treated with passive hemodialysis. The diagnoses cardiac disease, type

2 diabetes mellitus, and postrenal causes of renal disease negatively influenced survival. In the case of postrenal causes this is probably due to the primary diagnosis (cancer of the lower urinary tract). The diagnosis glomerulonephritis was, in our population, strongly associated with a longer survival.

Patients not treated with RRT also had a high mortality rate. Of the 196 patients in this group, 112 (65 male and 47 female) died within the observation period. Again, cardiac diseases, but also malignancies, were associated with a poor prognosis. A better survival was found in the group of patients with postrenal causes of renal disease. Probably due to selection.
Overall survival was substantially influenced by comorbidity, as is illustrated by the Kaplan-Meier survival plot based on the Charlson index for the total group of patients (Figure 3.1).

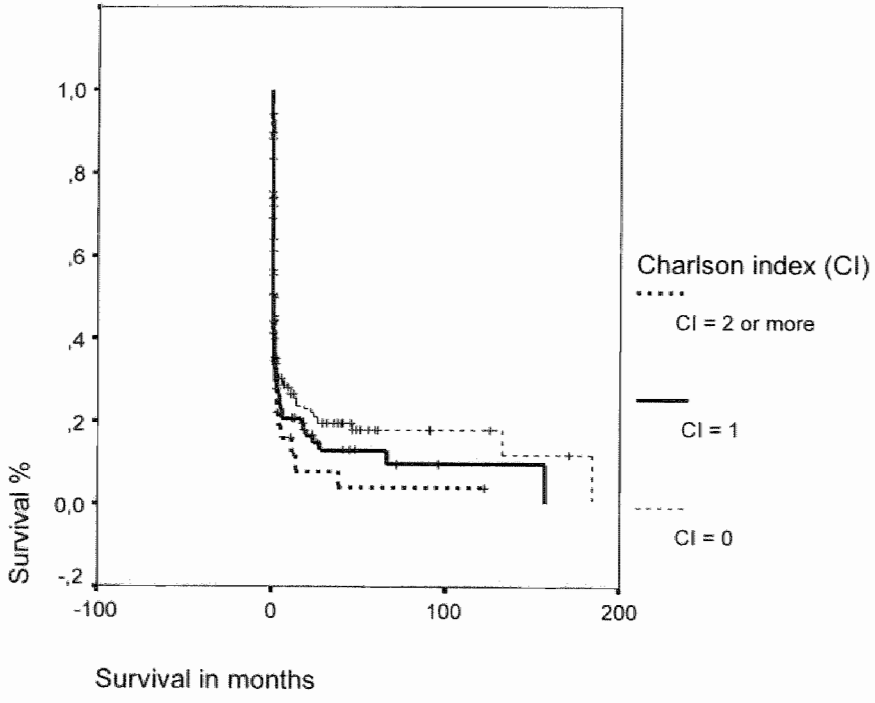

Figure 3.1 Overall survival by Charlson index

Discussion

Our group of elderly ESRD patients is characterized by a striking male preponderance. This is in sharp contrast with the distribution of the sexes in the general elderly population.
This altered distribution is most likely due to the importance of atherosclerotic diseases in the etiology of ESRD.

The incidence of ESRD found in our elderly population (2.2 per 1000 individuals) is higher than that reported in the literature.[10] This is mainly due to the fact that the incidence of renal failure in the elderly is normally estimated in patients accepted for, or already in, renal replacement programs. Our higher incidence may still be an underestimation, due to the fact that we based our investigation on laboratory data obtained from hospitals with dialysis facilities. In our region, a general physician can obtain laboratory investigations from laboratories not situated in a hospital. Patients who, for one reason or another, were not referred to the hospitals participating in our study were not included in our search.

The number of patients from whom a renal biopsy was taken to establish the diagnosis was very low in our population. However, this reluctance of nephrologists to perform renal biopsies in elderly patients seems to be common practice.[4, 22,23]

The most common reported causes of ESRD in the elderly are vascular renal disease, presumably secondary to hypertension, and diabetes. The central role of hypertension is widely accepted.[4,24,25]

Although vascular disease is reported to be one of the main causes of ESRD in elderly patients, the number of patients we found with exclusively cardiovascular events in their medical history was remarkably small. The number of patients who had events from other diagnostic groups, especially GI-tract and urogenital tract diseases, was extensive. This finding suggests that ESRD is a disease that afflicts patients towards the end of their life, when they already suffer from a number of diseases that impair their health and general condition, superimposed on the anatomical and physiological changes brought on by aging.[26]

The incidence of acute renal failure in our study increased with age. The highest incidence of acute renal failure was found in the group of patients above 80 years of age. This introduces the possibility of selection bias. The rapid deterioration of a patient could have been the reason for a hospital admission, whereas more slowly progressing renal failure in an elderly patient could merely have been considered a sign that he/she was approaching the end of life, thus not leading to a referral.

In support of this hypothesis is the finding that 106 of the 112 patients with acute renal insufficiency met the criterion for ESRD while in the hospital. Most were admitted at the time this occurred or just before. In all, only 70 patients were admitted to the hospital after the diagnosis of ESRD had been made.

Our data suggest that age is a factor for withholding treatment. Fifty percent of the patients in the youngest age group began RRT, whereas only 20% of the patients in the group 80 years of age and above did. Ageism in ESRD treatment has been reported in a number of European countries.[27-29] Several surveys among different groups of physicians suggest that this "inequality" is partly due to physician bias.[17, 25]

While age is often considered to be the main factor in deciding whether or not to start RRT, comorbidity may play an even more important role.[30]

The majority of our patients were treated with passive center dialysis. Only 14% of those treated underwent peritoneal dialysis. Throughout the world there is a wide variation in the type of RRT offered to elderly patients. In Australia, New

Zealand, and France there seems to be a clear preference for home peritoneal dialysis for patients older than 60 years.[31,32]
The percentage of elderly patients undergoing hemodialysis versus chronic peritoneal dialysis (CAPD) in our survey is comparable to that in the United States.[10] In spite of any global differences, peritoneal dialysis is considered the treatment of choice for dialysis of the elderly, particularly those with cardiovascular disease or hemodynamic instability.[33-35] Our data illustrate this statement by showing a better initial survival of patients treated with CAPD. These patients undoubtly were selected for CAPD based on better initial performance. Overall survival after slightly more then 2 years was 50%. A highly significant statistical difference was found in mean survival between patients who underwent acute RRT and those who chose to enter a RRT program (106 vs. 1091 days, respectively, $p=0.000$). Our data, therefore, confirm reports that early death in dialysis is often the result of late referral.[36,37] The majority of our patients was also only referred to the hospital just before or at the time they met the criteria for ESRD. Thus, early recognition of impaired renal function and early referral seem to be very important in the elderly patient.
After our first analysis, a number of questions remain unanswered. First of all, it is unclear which patient characteristics were used to base a treatment decision on in our patient population. Secondly, it has yet to be determined which prognostic factors for patient survival can be found in both the RRT and the non-RRT groups. Third, based on our collected data, methods need to be developed that will allow us to estimate the chance of successful decision making (i.e., whether or not to start RRT).
Evidence-based decision-making is not only in the interest of the patient and the patient's family, but it is also important for physicians and dialysis staff. For these reasons, our group is currently conducting additional and extensive analyses of our present and new data.

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Chapter 4

Treatment selection criteria and prognostic factors in elderly patients with end-stage renal disease

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Submitted for publication

Abstract

Background

The demand for renal replacement therapy (RRT) for elderly patients with end-stage renal disease (ESRD) is increasing worldwide. The rising incidence of ESRD in the elderly is generating a great deal of controversy and debate about the appropriateness of spending scarce resources for expensive medical techniques on a group of patients with a limited life expectancy. Though not always explicitly, age is, indeed, one of the factors used to ration dialysis treatment. Another criterion for selection is comorbidity. We conducted a retrospective survey to assess the percentage of elderly ESRD patients enrolled in RRT programs. We also attempted to determine what factors are involved in selecting elderly patients for RRT and what prognostic factors for survival are found in elderly patients on RRT.

Methods

A retrospective study was carried out on 274 patients, aged 65 years and older who developed ESRD in 1992 and 1993. The patients were recruited from four hospital-based renal units. Case finding was done using the computerized laboratory files of the participating hospitals. During this inclusion period 96 patients were enrolled in RRT programs and 178 were no treated with RRT.
Survival was assessed until 31-12-1999 (end of the study).

Results

In the group of patients who entered RRT and died in the study period, mean survival was 570 days in the age group 65–70, 641 days in the age group 71–75, 351 days in the age group 76–80, and 102 days in the group patients over 80.
In patients that not were treated by RRT mean survival of those who died during follow-up was for the different age groups 418, 370, 322, and 221 days respectively. Survival was dependent on age and comorbidity. In the group treated with RRT, the causative diagnosis of nephrosclerosis and age influenced the prognosis. Logistic regression analysis showed that selection for treatment was significantly associated with serum creatinine, with the causative diagnosis of glomerulonephritis, and with functional problems in urine production.

Conclusion

Selection for RRT does occur in medical practice. Selection criteria can be divided into medical criteria (serum creatinine), nephrological diagnoses (glomerulonephritis and nephrosclerosis), and existing comorbidity. The ability to perform activities of daily living, mobility, and the presence of a partner also influence treatment decisions. Finally, age and the length of renal history both influence survival, whereas the application of RRT does not.

Introduction

Chronic renal replacement therapy (RRT) programs have gradually become accessible to elderly patients over the last ten years. Improvements in diagnostic and therapeutic procedures for patients with cardiovascular diseases have led to better survival. However, this has also contributed to an increase in the number of patients with late renal complications of vascular diseases. Patients with type 2 diabetes mellitus with vascular complications are now admitted to chronic RRT programs. Renal transplantation is still mainly confined to younger patients, due to a shortage of donor organs. All of these factors have led to a situation in which elderly patients comprise a steadily increasing segment of the patient population in RRT programs in North America, Europe, Australia, and New Zealand.[1-5]

Elderly patients with end-stage renal disease (ESRD) can be divided into two separate groups.[6] The first group consists of patients who adjust very well to dialysis with a high quality of life or who appear to be satisfied with a reasonable quality of life that may, however, be unacceptable to a younger patient.[7,8] The second group is characterized by comorbidity and impaired functional capacity. Some of these patients improve markedly with dialysis.[9] Others, however, deteriorate rapidly.

Renal replacement therapy is expensive, and treatment capacity is not unlimited. Patient selection is, therefore, widely practiced.[10-13] Physicians often mention the estimated medical benefit from dialysis for the individual patient as the most important criterion in the decision to begin dialysis. Age, in itself, is not an appropriate independent criterion in this decision.[14] Non-referral to nephrologists by the general practitioner and non-acceptance by nephrologists both seem to occur.[13,15-19] Thus, not all patients are referred or accepted for RRT. However, no clear objective criteria have yet been defined for patient selection. Dialysis is considered inappropriate for patients with a poor prognosis, especially those with multiple organ failure, non-uremic dementia, malignancies and metastatic disease, or debilitating neurological diseases.[20] Most elderly ESRD patients die of a cardiovascular disease.[2,21-24] The second most common cause of death in the U.S., however, is withdrawal from dialysis, indicating the burden that renal failure and RRT inflict on the elderly patient.[25,26]

In this retrospective study, we address three questions: (1) What percentage of elderly ESRD patients is enrolled in RRT programs? (2) What are the main factors involved in selecting elderly patients for RRT? (3) What are the prognostic factors for survival in elderly patients on RRT, as well as in those not on RRT?

Subjects and methods

We retrospectively studied the incidence of ESRD, the clinical data of elderly patients with ESRD, the percentage of elderly patients enrolled in RRT programs, and the survival of ESRD patients with and without RRT. To facilitate this, a search was first conducted of the laboratory records of the four hospitals with dialysis facilities in our region (Laurentius Hospital Roermond, Maasland Hospital Sittard, Atrium Hospital Heerlen, and the University Hospital of Maastricht) for patients 65 years of age and older with a serum creatinine of at least 400 μmol/l (4.5 mg/dl), measured between January 1, 1992 and December 31, 1993. Because we were interested in the process of selection for ESRD treatment, we excluded all patients who developed ESRD before January 1, 1992, the beginning of the observation period. To assess the survival of our patient group, we made great efforts to determine the clinical outcome of these patients up until January 31, 1999, the end of the study.

The four participating hospitals are situated in the South Limburg region of the Netherlands. This region has a total population of 1.25 million inhabitants and has borders to the south, west, and east with Belgium and Germany. Insurance policies do not allow medical treatment of patients across the border. Therefore, this region is, in every respect, well-defined. The population served by these four hospitals is about one million persons. All laboratory data could be retrieved from computerized files of the hospital information systems. The hospital laboratories perform tests for inpatients, for outpatient clinics, and for all primary care physicians in the region.

The medical files of the patients were studied and data were extracted regarding age, gender, socioeconomic status, functional status, medical history, primary renal diagnosis, comorbidity, medical interventions, and clinical course. Medical history and comorbidity were entered following the International Classification of Diseases, 9th revision, Clinical modification (ICD9-CM).[27]

The period between the first indication of impairment of renal function and the moment the serum creatinine reached a value of at least 400 μmol/l was referred to as the renal history.

A short renal history (<4 weeks) was defined as acute renal failure; a longer renal history was considered to be chronic renal failure. In every patient creatinine clearance was calculated using the Cockroft and Gault formula.[28]

In the case of RRT, we discriminated between acute therapy, when therapy was started within 4 weeks after reaching a serum creatinine of 400 μmol/l or higher, and non-acute therapy, when it started after 4 weeks of the onset of ESRD.

To assess the severity of comorbidity, we calculated for each patient the Charlson index for comorbidity.[29] This is a good, validated scoring system for comorbidity and prognosis based on 1-year mortality rates of 19 frequently occurring internal diseases. Moderate or severe renal impairment was not scored for our patients since it was the primary disease (Table 4.1). The height

of the score is determined by the relative mortality risk within one year after a clinical admission for these diseases.

Table 4.1 Charlson weighted index of comorbidity

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

The functional status of the patients was investigated by making an assessment of each patient's ability to perform activities of daily living, of his/her mobility, and of urinary continence. For this we used Katz' scale of basic activities of daily living (ADL; bathing, dressing, toileting, transferring, and feeding).[30] In each of these five categories, three ratings were possible: good, able to perform with help, and complete dependency. Possible ratings for mobility were: good mobility including walking stairs, good mobility, mobility with aid or with a walking device, bed/chair only, and bedridden. The socio-economic status of the patients was investigated, by collecting data on living conditions, presence of a (supporting) partner and need for informal and/or professional help.

Finally, data were collected on urinary continence in our patient population. This was done because, in previous investigations, we had found that urinary continence is a prognostic factor for clinical outcome in elderly patients.[31] In this category, ratings were: complete incontinence, some incontinence, little incontinence, the use of some kind of catheter, the presence of a urostoma and, given the special group of patients we studied, anuria.

Statistical analysis

All statistical analyses were made using SPSS for Windows 7.5 (SPSS Inc., Chicago, IL, USA). Some of the analyses were performed by the Department of Methodology and Statistics of the University of Maastricht.
Data are presented as the mean value ± SD or number (percentage). Student's *t*-test was used to compare continuous variables; for categorical variables, the chi-square test or, when appropriate, the Fischer exact test was used.

For ordered categorical variables, such as scores or number of comorbid diseases, the chi-square for linear trend was used. Two-sided p-values not greater than 0.05 were considered significant.
For the clinical endpoint RRT, odds ratios (OR) are reported. All significant characteristics were entered into a logistic regression, with RRT as the dependent variable, using a stepwise, backward selection of variables. Only significant variables ($p<0.05$) were kept in the model. Results are given as odds ratios for treatment with RRT. To determine mean and median survival we excluded the patients still alive at the end of the study, because it is not good possible to determine mean survival in the presence of censored cases. The survival plots are drawn for the patients who died during the study.
The study was approved by the medical ethics board of the University Hospital of the University of Maastricht.

Results

Patients

With our retrospective search of the laboratory records we found a total of 567 patients who met the criteria of a serum creatinine of at least 400 µmol/l and age 65 years or older. We were able to retrieve hospital records from 331 patients with sufficient data for this study. The clinical characteristics of these patients have been described earlier.[32] Only patients who developed ESRD during the observation period were included. Our survey thus comprises data from 274 patients, 164 male and 110 female. The characteristics of this patient group are summarized in Table 4.2.
The mean age of the patients on RRT was significantly lower than that of patients not treated. Serum creatinine was higher in the treatment group and, consequently, the creatinine clearance computed with the Cockroft and Gault formula is lower. Body mass index was significantly higher in the group of patients not treated with RRT. Pulmonary edema was seen more often in the group of patients not treated with RRT, although the difference is not significant.

Medical history

A total of 828 medical events were mentioned in the medical histories of our 274 patients. In the untreated group, six patients had no medical event, as compared to four patients in the RRT group. The mean number of medical events in the total patient population was 3 events with a standard deviation of 1.6.
Substantially more events were recorded in the group of patients not treated with RRT, although no statistically significant difference was found in either the total number of events or the number of events in the subgroups.

Table 4.2 Basic clinical characteristics of the patient groups studied.

	RRT	No RRT	Chi-square linear trend
Number of patients	96	178	
-- male	56	108	
-- female	40	70	n.s
Median age	72 (65 - 92)	75 (65 - 92)	n.s.
Mean age	72.86 (SD 5.59)	75.80 (SD 6.89)	$p < .005$
Age groups (years)			$p = .003$
64 – 70	39 (41%)	48 (27%)	
71 – 75	26 (27%)	44 (25%)	
76 – 80	20 (21%)	43 (24%)	
> 80	11 (11%)	43 (24%)	
Serum creatinine	725 µmol/l (SD 316.76)	549 µmol/l (SD 203.85)	$p < .005$
Body weight (mean)	68.1 kg (SD 11.3)	69.9 kg (SD 12.68)	n.s.
Body mass index (BMI)	23.9 kg/m^2	24.5 kg/m^2	$p = .006$
Systolic blood pressure	153.7 mmHg (SD 32.1)	142.3 mmHg (SD 38.0)	n.s
Diastolic blood pressure	83 mmHg (SD 17.7)	78.7 mmHg (SD 19.5)	n.s
Heart rate	88.3 b/min (SD 17.8)	89.4 b/min (SD 20.17)	n.s.
Irregular pulse (no.pts)	8	13	n.s
Pulmonary edema (no.pts)	24	44	n.s
Partner	61	86	$p = 0.16$
No Partner	35	92	OR= 1.864 CI: 1.121-3.102

As expected, we found a relatively high number of cardiovascular diseases. Seventy-seven patients had one cardiovascular event in their medical history (33 in the RRT group and 44 in the untreated group). Two cardiovascular events were found in 54 patients (13 in the RRT group and 41 in the untreated group). Three or more cardiovascular events were found in the medical history of 24 patients (8 in the RRT group and 16 in the untreated group). Eighty patients, however, had not had a single cardiovascular event in their medical history (26 in the RRT group and 54 in the untreated group).
Urogenital tract diseases, gastrointestinal tract diseases, malignancies, and endocrinological diseases were also extensively represented, all of them more frequently in the group of patients not treated with RRT.

Comorbidity

In 33 patients (9 untreated and 24 treated), no comorbidity was present at the moment ESRD was diagnosed. One comorbid disease was present in 98 patients, two were present in 99 patients, and three in 44 patients. The difference in the number of comorbidities between treated and untreated

patients was statistically significant (test for linear trend $p<0.005$). Cardiac, gastrointestinal tract, and urogenital tract diseases were seen as frequently in the treated group as in the untreated group. There were more patients with peripheral vascular disorders and pulmonary diseases in the untreated group. This difference, however, was not statistically significant.
We calculated the Charlson index for comorbidity for the members of our patient population. In the total group of patients, 52% had a score of 0, 30% a score of 1, and 18% a score of 2 or higher (Figure 4.1). The difference in frequency of the Charlson scores in treated and untreated patients reached a p-value of 0.004 (chi-square for linear trend).

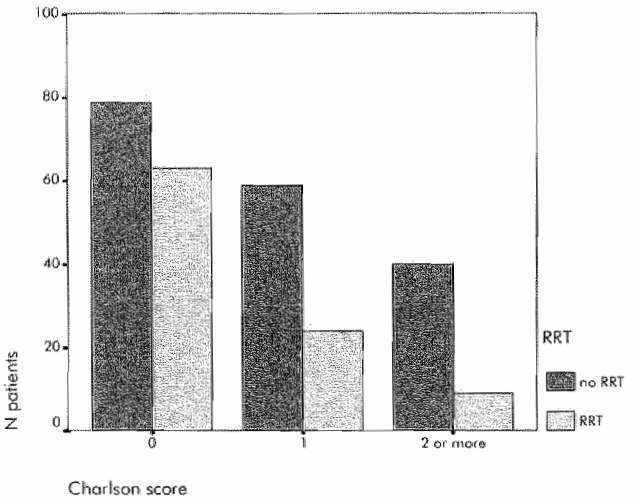

Figure 4.1 Charlson score patient groups

Renal history

A wide range in renal history was found. In 111 patients (41%), renal history was short: ESRD developed within one month, in 102 patients even within just 2 weeks. Thus, in a substantial part of our population of elderly patients, we found a more or less acute onset of renal failure. The percentage of patients with acute renal failure tended to increase with age. In the youngest age group (65-70 years) 29 patients (39%) had a renal history of 1 month or less. (Table 4.3) In patients 80 years of age and older, 51% had a short renal history.
In contrast, in many patients there was a slow development of the renal disease. In 121 patients, renal history renal history was 1 year or more; in 64 patients the renal history even exceeded 5 years. The largest percentage of patients with a long history (•1 year) - 52% - was found in the youngest age group. In the group of patients over 80 years of age, this percentage was 40%. In 15 patients renal history could not be computed due to missing data.
Of the patients who died during the inclusion period mean survival was determined. (Table 4.3, figure 4.2) The best survival was seen in the group with

the longest renal history, in the youngest age group. Furthermore, survival is strongly influenced by age; a higher percentage of patients from the higher age groups die and the mean survival has a tendency to be shorter.

Table 4.3 Renal history and survival by age group in 259 elderly patients with ESRD

Renal history	Age groups	N	Pts. died (%)	Mean survival (SD)
0-14 days	65-70	26	9 (35)	105.67 (205.18)
	71-75	26	14 (54)	64.43 (157.73)
	76-80	26	15 (58)	15.07 (20.77)
	>80	28	22 (79)	21.41 (28.48)
15-30 days	65-70	3	1 (33)	321.00
	71-75	1	1 (100)	7.00
	76-80	0	0	
	>80	1	1 (100)	4.00
31-182 days	65-70	7	4 (57)	44.25 (55.01)
	71-75	6	4 (67)	26.75 (38.08)
	76-80	7	5 (71)	17.20 (8.96)
	>80	4	2 (50)	8.00 (11.31)
183-365 days	65-70	0	0	
	71-75	1	1 (100)	13.00
	76-80	1	0	
	>80	1	1 (100)	7.00
1-2 years	65-70	7	5 (71)	71.80 (112.60)
	71-75	6	1 (17)	108.00
	76-80	2	1 (50)	2.00
	>80	2	0	
2-5 years	65-70	13	5 (38)	25.20 (29.65)
	71-75	12	6 (50)	42.33 (67.14)
	76-80	11	9 (82)	10.22 (3.03)
	>80	4	2 (50)	3.50 (3.54)
> 5 years	65-70	19	5 (26)	260.60 (341.88)
	71-75	16	8 (50)	22.50 (27.14)
	76-80	12	8 (67)	29.13 (27.20)
	>80	17	12 (71)	9.75 (13.31)
Total		259	142	

Renal history of 15 patients could not be computed due to missing data.

Renal diagnosis

In the records we studied we found a total of 409 diagnoses related to ESRD. In 164 patients (60%), one renal diagnosis was made. Two diagnoses were reported in 88 patients (32%). In 22 patients (8%), three or more diagnoses were reported. This abundance of diagnoses was probably due to the fact that in only

11 patients a renal biopsy was performed to establish a clinical diagnosis of the ESRD.
The total number of diagnoses made in the group of patients treated with RRT was 148 versus 261 in the untreated group. The difference in the number of diagnoses between the two groups was statistically significant (p=0.001).
Cardiac diseases, postrenal causes, and dehydration were all less often present in the group of treated patients (Table 4.4). Glomerulonephritis and nephrosclerosis, not surprisingly, were significantly more often seen in the group of patients treated with RRT.

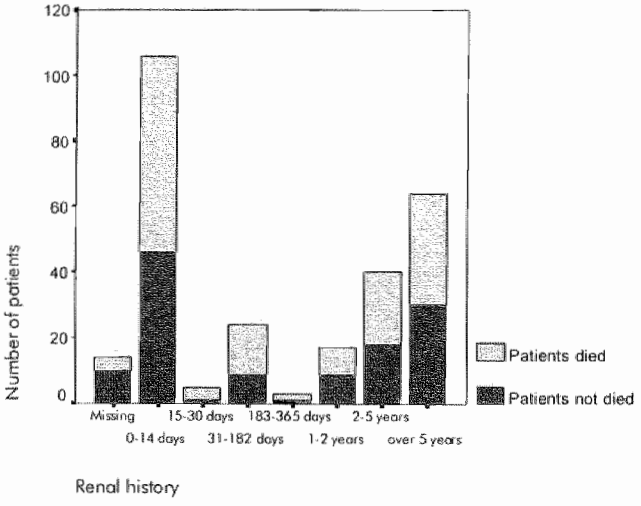

Figure 4.2 Renal history and survival in 259 elderly patients with ESRD

Functional status

It was possible to assess the activities of daily living of 268 patients from the data in the medical records.
In the categories bathing, dressing, and transfers, we found a significant difference between the patients treated with RRT and those not treated in favour of the treated group.
For 267 patients an assessment of mobility could be made. Again, we saw a trend in favour of the patients treated with RRT. When we divided mobility into two categories - good or impaired - the difference between the two patient groups reached statistical significance.
The same picture emerged in the evaluation of urinary continence. Patients not treated with RRT were more often incontinent, had a catheter, or were more often anuric than the treated group. We recoded this variable into four dichotomous variables: (1) urinary problems (no problems versus problems), (2) urinary continence (continence versus incontinence), (3) urinary catheter (catheter versus no catheter), and (4) urine production (production versus no production.). For urinary problems and continence, we found significant

differences, both with a p-value below .005. The odds ratios were .335 (95% CI .191-.587) and .092 (95% CI:.028-.309), respectively.

Table 4.4 Renal diagnosis.

Renal diagnosis	RRT	No RRT	chi-square	Odds ratio*
Cardiac disease	10	38	p=0.023	OR=0.428 (0.203-0.904)
Vascular disease	25	33		
Hypertension	30	31	p=0.009	OR=2.155 (1.207-3.849)
Postrenal cause	8	45	p=0.001	OR=0.269 (0.121-0.597)
Glomerulo-nephritis	16	4	p=0.000	OR=8.7 (2.818-26.857)
Sepsis	5	17		
Postoperative	11	20		
Dehydration	2	30	p=0.000	OR=0.105 (0.025-0.449)
Nephrocalcinosis	7	11		
Nephrosclerosis	14	12	p=0.035	OR=2.362 (1.045-5.337)
Polycystic disease	4	1		
Nephrectomy	1	0		
Unknown	15	19		
	148	261		

OR= odds ratio, in brackets 95% confidence interval
OR before entered in logistic regression

Finally, we investigated the social context of our patient group, i.e., whether they lived independently, alone or with a partner, or in some kind of care-giving situation, indwelling with their children, in a home for the elderly/nursing home or in a cloister. Though the untreated patients tended to be more in need of care than the treated patients, the difference was not statistically significant. In the group of treated patients, there were significantly more living together with a partner than living alone (p=0.016). We found an odds ratio of 1.864 (95% CI:1.121-3.102), indicating that patients with a partner have a greater chance of being accepted for RRT than patients who live alone (Table 4.2).

Logistic regression analysis

In a univariate analysis of our patients comparing RRT and no RRT, we found 13 variables with a significant difference, age, serum creatinine, BMI, presence of a partner, number of comorbidities, causing diagnoses cardiac, hypertension, postrenal causes, glomerulonephritis, dehydration and nephrosclerosis, urine problems and continence. Since the dependent variable is treatment (yes or no), a dichotomous variable, we performed a logistic regression analysis to see which of the characteristics were the most important. Backward selection of the variables was used.

The reported odds ratios are per unit of the independent variable, except for serum creatinine, where we reported the OR per 1000 units in order not to lose this coefficient in our model.
In this way, we obtained an OR of 26.6 for serum creatinine, an OR of 6.5 for glomerulonephritis, and an OR of 1.7 for patients with a urinary catheter. ORs larger than 1 mean that more of these patients are selected for RRT. For all other variables, an OR below 1.0 was found. Urinary incontinence, for instance, had an OR of .098, indicating an almost ten times smaller chance of being admitted to a RRT program. All ORs are given in Table 4.5.

Table 4.5 Results of logistic regression analysis

Variable	Significance	OR	
Creatinine	0.000	26.600	(6.233-113.515)
Cardiac cause of ESRD	0.007	0.311	(0.133-0.725)
Postrenal cause of ESRD	0.000	0.095	(0.031-0.290)
Glomerulonephritis	0.009	6.479	(1.580-26.560)
Dehydration	0.002	0.094	(0.020-0.434)
Incontinence	0.000	0.098	(0.027-0.349)

OR= odds ratio, in brackets 95% confidence interval

Survival

Eight patients in the treated group were still alive at the end of the study. Eight patients in the treated group were still alive at the end of the study, five in the youngest age group, the other three in the higher age groups. A comparison of the characteristics of these 8 patients with the 88 patients who died during this follow-up period is difficult due to the skewness of the distribution. Moreover, the moment we ended the follow-up was necessarily arbitrary. For the dichotomous variables, we only found a significant difference for nephrosclerosis ($p=0.015$, OR: .128, CI: 0.028-0.595). For the continuous variables, only age reached significance (T-test: $T=-1.995$, $p=0.049$).
Overall survival was influenced by age. Survival of the patients who died during the study are shown in Table 4.6.
In all but the highest age group mean and median survival is better in the patients who underwent RRT in comparison to the patients who did not receive renal replacement therapy. In patients over the age of 80 years, mean survival is better in the group not treated patients. Treatment gives in this age group only a slightly better median survival. In figure 4.3 the survival curves of the age groups are shown for all patients who died during the study.
Acute onset of ESRD in the elderly was accompanied by an increased mortality. A longer and more gradual onset of renal failure, with the possibility of a timely onset of treatment, was characterised by a better patient survival (Figure 4.4).

However, when renal history was more than 5 years, there was an increase in the number of patients dying during the follow-up period (Figure 4.4).

Table 4.6 Mean and median survival of the patients who died in the study period

	RRT	No RRT
Age = 65 - 70		
mean survival	570	418
median survival	598	321
Age = 71 - 75		
mean survival	640.6	369.5
median survival	541	132.5
Age = 76 - 80		
mean survival	350.8	321.5
median survival	47	15
Age > 80		
mean survival	102.2	221.2
median survival	70	16

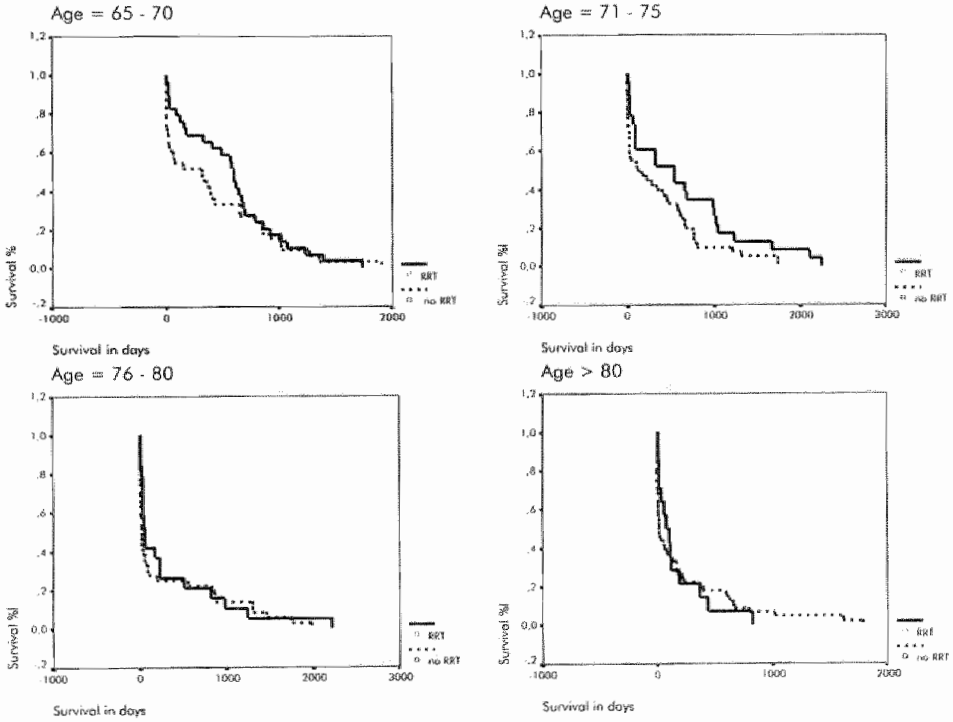

Figure 4.3 Survival and age

In each age group, the influence of comorbidity was clearly visible. Survival was shorter within each age class when a higher Charlson score was present (Figure 4.5).

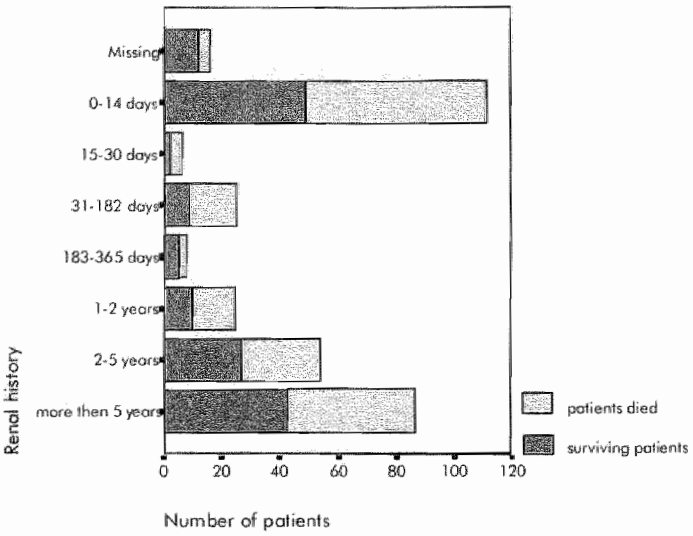

Figure 4.4 Death in relation to renal history

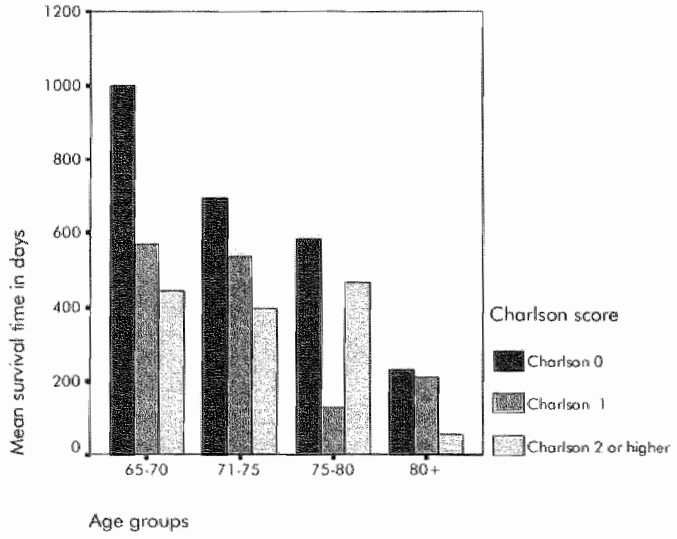

Figure 4.5 Survival in relation to Charlson index

Conclusions

We compared elderly patients with ESRD who underwent RRT with those who did not and found a number of differences. It seems reasonable to suggest that these differences were at least partly due to selection by the nephrologists in charge of the RRT departments of the participating hospitals.

From our findings, it appears that factors that favour treatment include a high serum creatinine, the causative diagnosis of glomerulonephritis and/or nephrosclerosis, younger age, lower body mass, a low Charlson index (indicating less comorbidity), and the presence of a partner. In contrast, dehydration, postrenal causes of renal impairment, cardiac causes of renal failure, and problems with the urinary tract appear to be factors that favour a no treatment decision. In a logistic regression model using a stepwise backward strategy, serum creatinine, the diagnosis of glomerulonephritis, and the need for a urinary catheter were the independent factors that favoured treatment. Nephrologists are probably not aware of all these factors when they are confronted with an elderly patient with ESRD. Nevertheless, it is conceivable that, especially in an elderly patient, the presence of a partner who clearly wishes to keep the patient alive can also influence the treatment decision. The importance of comorbidity is not surprising; in other disciplines as well (e.g., oncology), decisions are based in part on existing comorbidity.[33] Interestingly, problems with urine production and continence are considered to be an expression of the poor condition of a patient. These findings are in line with the finding that urinary incontinence is associated with a poor prognosis in elderly in-hospital patients.[32]

Although age is generally not considered to be a selection criterion, it did seem to influence our study population, not only in the treatment decision but also in the survival of treated patients. Treatment is more often offered to younger patients than to older patients, resulting in a significant difference in the mean age between treated and untreated groups. Survival is influenced by age. Overall survival was best in the youngest group we studied, which is in accordance with the literature.[34-36] Treatment resulted in better survival in all but the oldest age group in our study, compared to the no treatment group. Given these results, it would seem appropriate to offer RRT to patients up until the age of 80 years. In patients over 80 years, comorbidity has to be considered as a major factor influencing survival since only patients with a low Charlson index were found to survive in our data.

Thus, for the eldest patients, RRT should only be attempted in those with no, or only minor, comorbidity.

One must bear in mind that ours was a selected population. It is widely known that elderly patients with ESRD are often not referred to the hospital by the general physician. This phenomenon probably influenced the finding that an acute deterioration of renal function in our population was most often seen in the eldest age group. A slow and gradual loss of renal function in this group is probably accepted as a hallmark of the end of life and does not usually lead to

referral. However, survival appears to be influenced by renal history. Patients with a long renal history and, consequently, a more gradual and less aggressive progression of their renal disease, are probably more suited candidates for RRT. It may be concluded that the "wrong" category of elderly patients is usually referred to the hospital, especially in the eldest age group.
Thus, selection of elderly patients for RRT does occur in daily medical practice, primarily on the basis of a high serum creatinine and the nephrological diagnoses of glomerulonephritis and nephrosclerosis, but also on coexisting comorbidity. Age also seems to play a role in the treatment decision, although nephrologists may not be fully aware of this selection criterion. The ability to perform activities of daily living, mobility, and the presence of a partner (operating as a "defender" of the patient's interests) are additional factors that are taken into account in treatment decisions. One must remain alert to any slow and gradual deterioration in renal function in elderly patients so that a timely intervention can be of benefit to this group of patients.

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Chapter 5

The illness burden of end-stage renal disease in elderly patients

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Submitted for publication

Abstract

Background

The incidence of end-stage renal disease (ESRD) in elderly patients is increasing. Elderly patients are often not suitable candidates for renal transplantation and are mostly treated by passive center hemodialysis. The resources for this type of renal function replacement therapy, however, are not unlimited, and there has been much debate about the appropriateness of using expensive medical techniques on a patient group with a limited life expectancy. Thus, it is inevitable that selection decisions for dialysis treatment are made in this patient category. In order to determine which medical factors should be taken into account when making these decisions, we performed a multicenter study to assess the impact of ESRD on elderly patients. We also investigated which beneficial effects can be expected from dialysis treatment for elderly patients.

Methods

A multicenter, longitudinal, comparative trial was performed from June 1, 1996 until June 1, 1997 on 16 ESRD patients selected for, but not yet on, RRT, 107 patients in stable condition on RRT, and 59 consecutive patients referred to the outpatient facility of the geriatric department. A follow-up survey of these patients was carried out in 2000. Baseline characteristics, medical history, and comorbidity were assessed in each patient and an extensive functional assessment was made regarding the impact of the disease on well-being.

Results

Patients on dialysis scored lower on mobility and on their functional performance of activities of daily living than did pre-dialysis patients and older control patients. The major impact of renal disease on elderly pre-dialysis patients was a deterioration of functional capability over a period of 3 months. Nevertheless, the sickness impact profile showed the patients on RRT as having the highest score. Although physical condition may improve as result of the treatment, the feeling of well-being does not. Because no signs of depression could be found in these patients, we speculated that their feeling of no longer being "in control" was the cause of this high score on the sickness impact profile.

The follow-up survey in September 2000 showed that over 52% of the RRT population had died since intake, compared to 38% of the pre-dialysis patients and 16% of the control group. These findings indicate not only the serious consequences of renal failure in elderly patients but also the limited effects of RRT on the survival of these patients.

Introduction

Hemodialysis was first used in the 1940s to sustain life in patients with acute renal failure. It soon became clear that while treatment was rather complicated, life could be prolonged, where otherwise death was swift and certain. Early dialysis regimens were often more focused on maintaining the fluid balance than on removing metabolic waste products. When tolerance of dialysis improved as a result of better permeability of the membrane, the substitution of bicarbonate for acetate in the dialysate, and the achievement of better fluid maintenance, the concept of dialysis shifted from merely sustaining life to striving for optimal patient survival. This is very important because, for many patients, dialysis therapy is not just a time bridge to renal transplantation, which is often considered the preferred form of renal replacement therapy (RRT). Many elderly patients are not suitable candidates for renal transplantation; others are unable to comply with the complicated medical regimens involved in transplantation. Still other patients have high antibody titers to many HLA class one antigens, or will never find the right donor kidney. Elderly patients are often not candidates for renal transplantation because of the physiological impairment of advanced age.

In the Netherlands, the number of patients receiving dialysis care doubled between 1985 and 1995.[1] Moreover, during this period, there was a considerable increase in the number of older and sicker patients accepted for dialysis.

Studies on quality of life are not conclusive. Some have found the quality of life of dialysis patients to be inferior to that of the general population.[2,3] Others have found no difference.[4]

The aim of the present study was to assess the impact of end-stage renal disease (ESRD) on elderly patients and to compare their quality of life with that of elderly patients without apparent renal impairment. We also sought to determine whether RRT reduces sickness impact in this population.

Study Design

A multicenter study on the impact of ESRD in elderly patients was conducted at four hospitals: the University Hospital in Maastricht, the Atrium Hospital in Heerlen, Maasland Hospital in Sittard, and Laurentius Hospital in Roermond. These four hospitals are the only centers with RRT facilities in the south-eastern part of the Netherlands.

In the period from June 1, 1996 until June 1, 1997, patients selected for, but not yet started on, RRT were asked to participate in this study. Due to the study design, which calls for a number of tests and the need to observe the patient over a long period of time, those patients who underwent acute RRT were not included in the study. To determine whether elderly renal patients improve in

physical and mental well being when treated with RRT, a number of elderly patients in stable condition on RRT in these four hospitals were also investigated. Elderly patients before initiation of maintenance dialysis often suffer from anorexia and weight loss, generalised weakness, encephalopathy, nausea and vomiting.[5] RRT may improve the physical condition of elderly patients. To determine whether physical recovery also leads to improvement of functional ability and the feeling of well being, and to assess the extent of this functional improvement, we compared the pre-dialysis and dialysis patients in this aspect with a number of elderly patients as a control group. We selected a group of consecutive elderly patients referred to the outpatient clinic of the Department of Medicine and Geriatrics of the University Hospital Maastricht. These control patients were included when no apparent impairment of the renal function (as measured by serum creatinine) was found. Data were collected on medical history, use of medication, and present (co-) morbidity. Baseline characteristics at the physical examination were recorded, and every patient was extensively interviewed with regard to mobility, their ability to perform activities of daily living (ADL), and their need for informal or professional care. In September 2000, we performed a follow-up survey to assess the clinical course of the patients originally included in the study.

Functional assessment

The functional status of the patients was determined by assessing each patient's ability to perform ADL, as well as his/her mobility and urinary continence. The Katz' scale of basic activities of daily living (bathing, dressing, using the toilet, getting in and out of bed, and eating) was used.[6] In each of these five categories, three ratings were possible: good, able to perform with help, and complete dependency. Possible ratings for mobility were: good mobility including walking stairs, good mobility, mobility with support or walking device, bed/chair only, and bedridden. Ratings for urinary continence were: complete incontinence, some incontinence, little incontinence, the presence of a catheter and the ability to handle this, the presence of a urostoma and, given the special group of patients we studied, no urine production at all.
In addition to ratings in these fields, the functional status of every patient was estimated using the Barthel index of activities of daily living[7]. Each patient was given an individual score in each category, and a total score was computed as well. Someone with a score of 16 or more was considered to be functionally independent. Those with scores of 15 or below were considered dependent.

Cognitive Function

Every patient was screened for cognitive disorders using the Mini Mental State Examination.[8] The MMSE is a widely used, brief screening tool for use at the bedside by physicians, nurses, social workers, or technicians. It tests time and space orientation, registration, attention, calculation, recall, and language. The sensitivity and specificity of the MMSE are adequate for detection of cognitive deterioration or dementia in a community as well as in a hospital population.

Functional health status

The most widely used functional status health questionnaire is the Sickness Impact Profile (SIP), developed in the late 1970s in the United States.[9] The SIP has been translated into many languages, including British English, Swedish, German, French, Danish, and Norwegian.[10] In 1985, a Dutch version of the SIP appeared.[11]
We decided to use a short version of the SIP, the SIP68. This instrument was developed in Maastricht and widely tested. It has proven to be a valid and reliable instrument for measuring health related functional status and is in every respect a good alternative to the original Sickness Impact Profile (Appendix II).[12] Most patients were able to fill out the questionnaire independently; however, when necessary, assistance was offered by a specialized trial nurse.

Functional observations

The specialized trial nurse observed the RRT and pre-dialysis patients and made an assessment of their feelings of helplessness, aggression, depression, physical or mental invalidity, and their degree of inactivity.
The BOP, an observation scale especially designed for elderly patients and commonly used in many Dutch geriatric departments, was used. The dialysis patients were observed during their stay in the dialysis department. The pre-dialysis patients were observed during their visit to the nephrology department and were also visited at their homes. During the observation period, we repeated this functional observation in 13 dialysis patients and 4 pre-dialysis patients after a period of 3 months.

Statistics

All statistical analyses were made using SPSS for Windows 7.5 (SPSS Inc, Chicago, IL, USA). Data are presented as mean values ± SD or number (percentage).
Student's *t*-test was used to compare continuous variables; for categorical variables, the chi-square test or, when appropriate, the Fischer exact test was used. For ordered categorical variables, such as scores, the chi-square test for linear trend was used. Two-sided p-values not greater than 0.05 were considered significant.
Survival plot was made by using the Kaplan-Meier method based on estimating conditional probabilities at each time point. Patients still alive at the end of the study were censored.

Results

During the observation period of 6 months, we collected data on 182 patients: 16 pre-dialysis patients, 107 dialysis patients, and 59 control patients. In the dialysis group, 95 patients were on chronic, passive center dialysis and 12 were on CAPD. Baseline characteristics of these patients are summarized in Table 5.1.

The number of pre-dialysis patients was very small. The main reason for this low number of patients was that we only could interview patients who were expected to start RRT within a short period of time. Patients who underwent acute RRT were not included. Acute onset of RRT is most often seen in the elderly population, as demonstrated in earlier investigations.
All three subgroups showed a male preponderance. Mean age was comparable in the pre-dialysis and dialysis groups. The outclinic patient population was notably older.

Table 5.1 Patient characteristics

	Pre-dialysis pts	Dialysis pts	Control pts
N (♂, ♀)	16 (10,6)	107 (60,47)	59 (38,21)
Mean age (years)	72.63	72.59	77.92*
65 – 70	8	41	9
71 – 80	5	56	27
≥ 81	3	10	23
Mean serum creatinine (μmol/l)	475	809*	94
Mean systolic blood pressure	152	141	151
Mean diastolic blood pressure	75	85	81
Mean body weight (kg)	74	78	68*
Social status	N (%)	N (%)	N (%)
Living with partner	8 (50)	66 (62)	26 (44)
Widowed	7 (44)	29 (27)	27 (46)
Divorced	1 (6)	3 (3)	5 (9)
Not married		9 (8)	
Living conditions			
Independently with partner	8 (50)	59 (55)	24 (41)
Independently alone	6 (38)	19 (18)	26 (44)
Indwelling with children/ home for the elderly/ monastery/ nursing home	2 (12)	30 (28)	9 (15)

* Difference statistically significant

Mean serum creatinine was much higher in patients on RRT than in those with ESRD but not yet on RRT. The mean serum creatinine in the control group showed only slightly impaired renal function, probably due to a functional loss caused by aging.
There were no large differences in mean systolic and diastolic blood pressure among the three groups, although mean diastolic pressure was slightly elevated in the patients on RRT.
Mean body weight was notably lower in pre-dialysis patients than in those on RRT. This is probably due to the poor physical condition of this group of patients.

A lower body weight was also found in the control group, most likely as a result of their higher age.
Most patients in both groups were living independently with their partner or alone.
Thirty patients in the dialysis group (28%), however, were living with their children or in a home for the elderly, indicating that they were in need of a certain amount of care.

Mobility and ADL-ability

In the pre-dialysis group, all patients had a reasonable degree of mobility. Twelve patients (75%) could walk independently and were able to climb stairs. In the group of dialysis patients, this was true of 60 %of the patients. Fourteen patients were in need of support and five were bedridden. In the group of elderly controls, 54 patients (93%) were able to walk independently (Table 5.2).

Table 5.2 Mobility

	Pre-dialysis patients		Dialysis patients		Control patients	
	♂ (%)	♀ (%)	♂ (%)	♀ (%)	♂ (%)	♀ (%)
Walking ability						
Independent incl. stairs	7 (70)	4 (67)	40 (67)	25 (53)	26 (68)	15 (71)
Independent	2 (20)	1 (17)	17 (28)	4 (9)	11 (29)	3 (14)
with aid	1 (10)	1 (17)	3 (5)	10 (21)		3 (14)
with support			4 (7)	3 (6)	1 (3)	
bed/chair				5 (11)		
Walking distance						
>50 m	6 (60)	4 (67)	39 (65)	18 (38)	31 (82)	
>10 <50 m	4 (40)		18 (30)	16 (34)	7 (18)	16 (76)
<10 m		2 (33)	3 (5)	13 (28)		5 (24)
Devices						
No devices	7 (70)	4 (66)	43 (72)	27 (57)	25 (66)	12 (57)
Walking stick	3 (30)	1 (17)	12 (20)	10 (21)	13 (34)	6 (29)
Other walking device		1 (17)	3 (5)	4 (9)		3 (14)
Wheelchair			2 (3)	6 (13)		

The walking distance they were able to walk differed between the groups, and this difference was statistically significant (p=0.001) in the female patient group. In the five categories of ADL-ability - bathing, dressing, using the toilet, eating, and getting in and out bed - 79% of the control patients were independent, compared to 90% of the pre-dialysis patients and 70% of the dialysis patients (Table 5.3). Three patients from the control group and four from the dialysis group were completely dependent in these activities. These four patients were all on passive center hemodialysis. Yet, there were no significant differences in ADL-ability between CAPD and hemodialysis patients. It is interesting to note

that patients in the pre-dialysis group were never completely dependent in these activities and that only two patients from this group were in need of help.
The mean score on the Barthel index did not differ significantly among the three groups of patients. The mean score was 17.47 (SD:2.10) in control patients, 18.75 (SD:1.91) in pre-dialysis patients, and 17.30 (SD:3.33) in dialysis patients. Only two patients (12.5%) in the pre-dialysis group had a score below 15. The highest percentage (26%) of patients with a score below 15 was found in the dialysis group (Figure 5.1). Thirteen of the 59 control patients (22%) had a total Barthel score below 15. Thus, the pre-dialysis group appeared to be quite a homogenous group with a good ADL and mobility status. After 3 months, there was no deterioration in status in this group.

Table 5.3 Scores on ADL-activities of pre-dialysis, dialysis and control patients

	Pre-dialysis patients		Dialysis patients		Control patients	
	♂	♀	♂	♀	♂	♀
Washing						
independent	8	5	43	32	30	16
with aid	1	1	15	13	6	3
dependent			2	2	2	1
Dressing						
independent	8	5	48	36	34	18
with aid	1	1	12	10	3	1
dependent			1	1	1	1
Using the toilet						
independent	9	6	58	42	38	19
with aid			2	4		1
dependent				1		
Getting in and out of bed						
independent	9	6	56	41	36	19
with aid			4	4	2	1
dependent				2		
Eating						
independent	9	6	59	46	38	20
with aid			1	1		
dependent						

Care was predominantly provided by the partner. In 43% of the patients (all groups), the partner was mentioned as the main caregiver. For male patients, this was true of 54% of the patients versus 21% in the female group (Table 5.4). In the group of control patients, 24% of the men were being cared for by their partner; this was true of 67% of the male patients in the pre-dialysis group and of 72% in the dialysis group. When a distinction was made between informal help, i.e., that given by children, neighbours, friends, etc., and formal care, i.e.,

provided by nurses or specialized caregivers, we found that 76% of all male patients and 81% of all female patients were in need of informal assistance. Formal assistance was provided to 61% of the male patients versus 75% of the female patients. Among the three groups of patients, the difference reached statistical significance in male patients when formal help was concerned ($p=0.005$) and in female patients in the case of informal assistance ($p<0.000$).

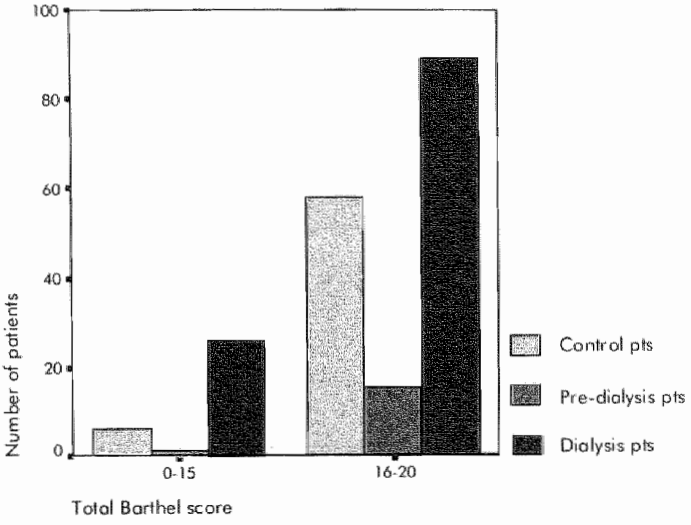

Figure 5.1 Total Barthel score

Cognition

The mean score on the MMSE in all patients was 25.47 (range 11-30). We found no difference among the three patient groups: mean MMSE in the control group was 25.59, in the pre-dialysis group 25.73, and in the dialysis patients 25.37. Some 155 patients had a score above 22 on the MMSE, indicating no cognitive problems. Only five patients scored 17 points or below, strongly suggesting cognitive impairment. All but one of these five patients were in the dialysis group.
The MMSE score showed a strong association with ADL-ability; in general, a better MMSE score was found in patients with a good ADL-ability (Table 5.5).

Table 5.4 Help providers. Use of formal and informal help of pre-dialysis, dialysis and control patients

	Pre-dialysis patients		Dialysis patients		Control patients	
	♂	♀	♂	♀	♂	♀
Informal help						
yes	8	5	50	43	23	10
no	1	1	10	3	15	10
Formal help						
yes	4	3	31	39	31	11
no	5	3	29	7	7	8

Data from one male pre-dialysis patient and one female control patient not obtained.

Table 5.5 ADL-ability and MMSE-score; association between scores on ADL-ability and MMSE

ADL-activity	Mean MMSE	Difference between groups (Anova)
Washing		
independent	26.29	p=0.000
with aid	23.67	
dependent	19.86	
Dressing		
independent	25.95	p=0.000
with aid	23.71	
dependent	18.00	
Using the toilet		
independent	25.70	p=0.000
with aid	19.71	
dependent	27.00	
Getting out of the bed		
independent	25.68	p=0.009
with aid	23.45	
dependent	19.50	
Eating		p=0.032
independent	25.53	
with aid	20.00	
dependent		

Data from one male pre-dialysis patient and one female control patient not obtained.

The same association was found between mobility and mean MMSE, although no statistical significance was reached. The best mean MMSE score was found in the group of patients with good mobility (mean MMSE: 25.73) in comparison

with patients with severely impaired mobility, which had a mean MMSE score of 23.60. A significant positive correlation was found between the MMSE score and the Barthel Index score (Spearman's rho:.268, significant at the .01 level, two-sided). No correlation was found between age and mean MMSE score. Nor did gender have any correlation with the score on the MMSE.
During the observation period, a second MMSE score was obtained from 39 patients: 23 dialysis patients, 11 pre-dialysis patients, and 5 control patients. There was no noticeable decrease in the MMSE score.

Sickness Impact

The mean score on the SIP68 was 20.09 in the control group. In the pre-dialysis group, we found a comparable score of 19.13, but in the dialysis group, the score was substantially higher, 26.44 ($p=0.001$) The mean SIP68 score in patients on RRT differed from that in patients on hemodialysis and CAPD: 27.10 versus 20.25; however, this difference was not statistically significant. The patients on CAPD had a substantially lower score on the item regarding somatic autonomy.
The frequency of scores on the SIP68 and on individual subscales is shown in Table 5.6.

Significantly higher total SIP68 scores were found in patients with impaired mobility ($p=0.000$), resulting in a positive correlation (Pearson correlation: 0.438 significant at the 0.01 level, 2-tailed). Dependency in ADL-activities also resulted in a higher total SIP68, again resulting in a positive correlation (Pearson correlation:0.592, significant at the 0.01 level, two-tailed).
These correlations are reflected in the finding that patients in need of much assistance (informal and formal) had significantly higher SIP68 scores (mean SIP of 21.39 versus 29.80, $p=0.000$). In this respect, it was not surprising to find a positive correlation between the MMSE results and the total SIP68 scores, with a Pearson correlation of 0.487, significant at the 0.01 level, 2-tailed.
Higher SIP68 scores were found in female patients than in male patients (mean SIP: 25.48 vs. 22.15) and in elderly patients (>75 years of age) compared to younger patients (<75 years). These differences, however, were not statistically significant.
In patients with urinary incontinence, higher SIP68 scores were found, in accordance with the frequency of involuntary loss of urine. In patients with complete urinary continence, we found a mean total SIP68 score of 21.61; in those with frequent urinary loss, the mean score was 29.44. In patients with complete incontinence, the mean SIP68 was 23.45. The difference between these three groups is statistically significant ($p=0.002$).

Functional observation

A functional observation was made in 14 pre-dialysis patients and 106 dialysis patients. The results are shown in Table 5.7. No significant differences could be found between the two patient groups. However, on each item, dialysis patients had higher mean scores than pre-dialysis patients.

As mentioned earlier, we repeated this functional observation in 13 dialysis patients and 4 pre-dialysis patients after a period of 3 months. No statistical significant difference was found between the two observations. Yet, a certain trend is discernable. In dialysis patients, the scores were generally lower at the time of the second observation, especially with regard to feelings of helplessness, physical and psychic invalidity, and inactivity. In addition, during the second observation, a higher score was found with regard to feelings of aggression.

Table 5.6 Frequency of score on the SIP68 and individual subscales

	Mean score	SD	% Zero scores	% Maximum scores	Difference between groups Anova
Somatic autonomy (number of items 17)					
control pts.	1.6	2.38	44.8	0	p=0.026
pre-dialysis pts.	1.47	2.26	53.3	0	
dialysis pts.	2.62	3.17	32.7	0	
Mobility control (number of items 12)					
control pts.	5.33	3.23	5.2	0	p=0.035
pre-dialysis pts.	4.93	4.40	26.6	13.3	
dialysis pts	7.40	7.24	5.6	0.93	
Mobility range (number of items 10)					
control pts.	3.76	2.60	13.7	1.7	p=0.211
pre-dialysis pts.	3.13	3.20	20	6.6	
dialysis pts.	4.29	2.91	16.8	3.7	
Social behavior (number of items 12)					
control pts.	5.98	2.85	5.2	0	p=0.000
pre-dialysis pts.	6.80	3.23	0	1.7	
dialysis pts.	8.38	2.69	0.93	9.3	
Emotional stability (number of items 6)					
control pts.	1.24	1.33	39.6	0	p=0.108
pre-dialysis pts.	1.00	1.31	53.3	0	
dialysis pts.	1.56	1.28	24.2	0.93	
Psych. autonomy and communication (number of items 11)					
control pts.	2.17	2.46	32.7	0	p=0.071
pre-dialysis pts.	1.0	2.18	33.3	0	
dialysis pts.	2.88	2.60	20.5	0	
Total SIP68					
control pts.	20.09	10.84	3.4	0	p=0.008
pre-dialysis pts.	19.13	13.87	0	0	
dialysis pts.	28.31	23.18	0	0	

Table 5.7 Functional observation of pre-dialysis, dialysis and control patients

Item	Pre-dialysis pts. mean score	Dialysis pts. mean score	Difference between groups Anova
Helplessness (scale 0-46)	4.57	7.50	p=0.294
Aggression (scale 0-10)	0.07	0.58	p=0.300
Physical invalidity (0-6)	0.64	1.42	p=0.256
Depressive behaviour (scale 0-6)	1.64	2.96	p=0.384
Psychic invalidity (scale 0-8)	0.29	0.50	p=0.418
Inactivity (scale 0-14)	3.0	4.96	p=0.037

In the pre-dialysis group, the second observation was characterized by higher scores on helplessness, physical invalidity, and inactivity, probably due to deterioration in the patient's condition. No increase in feelings of aggression was encountered in this group.

Clinical course

In due course, all but one pre-dialysis patient entered a RRT program. That one patient refused to. All other patients underwent passive center hemodialysis.
By September 2000, 6 patients (37.5%) from the pre-dialysis population had died. Fifty-six patients (52.3%) from the dialysis population died between the intake date and September 1, 2000. Control patients had a much better prognosis over time: 50 patients were still alive at the end of the study and only 9 (16.3%) died during follow-up. The difference between the groups was highly significant (p=0.000).
The mean survival of the pre-dialysis patients who died was 410.3 days; for the dialysis patients this was 565.5 days. The six control patients who died had a mean survival of 431.6 days. Survival of all patients until the end of the study is depicted as a Kaplan-Meier survival plot in Figure 5.2.
Neither survival rate nor mean survival was different in CAPD patients versus hemodialysis patients; however, the small number of patients on CAPD makes it impossible to draw conclusions from this result.

Discussion

Renal failure in elderly patients is a serious condition with a high morbidity and a bad prognosis quo ad vitam. Dialysis patients are worse off in terms of mobility and ADL-ability than control patients, even those who are older than they are. Consequently, they are in need of more help, informal and professional, than control patients and even pre-dialysis patients. In male patients especially, the disease places a heavy burden on the partner.

In spite of the fact that our group of control patients was significantly older than the patients with ESRD, mortality was much higher in the latter group. Survival in the pre-dialysis patients was probably somewhat better in this survey due to the fact that patients who entered acute RRT were not included. Acute onset of RRT in elderly patients is associated with a poor prognosis, as we reported before.[13]

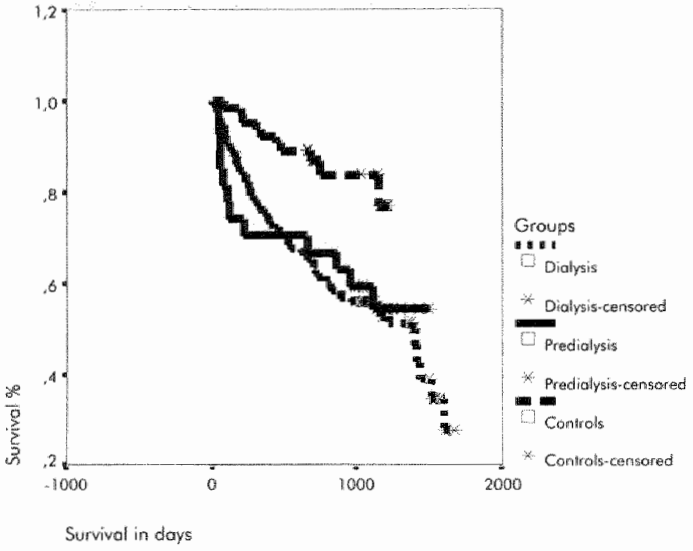

Figure 5.2 Survival of a predialysis patients, dialysis patients, and controls.

Nevertheless, patient characteristics of the group of pre-dialysis patients indicate the major impact of renal failure in the elderly. These patients have a lower body mass and show rapid deterioration, as shown in the functional observation scale. At the same time, in comparison with dialysis patients, they score well on mobility, ADL-ability, and cognition. This is most likely the result of selection. Only patients who perform well are selected to enter RRT within a short period of time. Patients in worse physical condition are likely to be included in a RRT program. Patients with limited mobility, ADL-ability, and most certainly cognition are more likely to be excluded from RRT.

Very interesting is the score on the sickness impact profile. Scores of pre-dialysis patients resemble those of elderly patients without renal disease. We did not expect this finding. Our hypothesis was that, due to the great impact of renal failure, pre-dialysis patients would suffer more from their disease. By improving their physical condition and restoring a feeling of well being, RRT was expected to lead to better performance on the SIP68. We can only speculate about the cause of these results. Functional observations gave no indication of more depressive feelings in RRT patients. One possible reason may be that these patients no longer felt in control when on RRT. The relatively high score of dialysis patients on the item "social behaviour" in the SIP68 lends some support to this explanation. Higher scores on mobility control and somatic autonomy also point in this direction. In any case, this finding is in sharp contrast to the

general notion that RRT not only prolongs life but also improves the quality of life.
It is possible that patients on CAPD have a better appreciation of the quality of their lives. Their mean total SIP68 score suggests as much. We were not able to find other differences between the two RRT modalities, but the percentage of CAPD patients was relatively low in our study population. Perhaps a greater effort should be made to include more elderly patients in CAPD programs.
The better appearance of the pre-dialysis patients is without doubt the result of selection. Only in the case of a good performing patient the decision can be made to postpone the start of RRT. Their better performance on mobility and ADL-tests, as well on the SIP68, makes it indeed tempting to do so. However their shorter survival, when started on dialysis confronts us with difficult to solve dilemma.
The group of pre-dialysis patients was very small in this study and we did not perform a formal follow-up procedure, making it hard to draw solid conclusions. However, it is clear that a proper timing of the onset of RRT is essential. The scarcity of dialysis facilities forces us to make choices. This seems to be a disadvantage of the well performing patient, who would probably do better on RRT when started earlier.

APPENDIX I Barthel Index

BOWELS
2 continent (for preceding week)
1 occasional accident (once a week or less)
0 any worse grade of incontinence (or needs enemas for continence)

BLADDER
2 continent (for preceding week) or able to manage any device (e.g., catheter and bag) without help.
1 occasional accident (once a day or less) or catheterised and needs help with device.
0 any worse grade of incontinence.

FEEDING, food placed within reach
2 able to cut up food, spread butter, etc. without help
1 needs some help cutting or spreading
0 needs to be fed.

GROOMING
1 independent washing face, combing hair, shaving, and brushing teeth (when implements are provided)
0 needs help.

DRESSING
2 independent putting on all clothes, incl. fastening buttons, zippers, etc. (Clothes may be adapted).
1 needs some help, but can do at least half
0 needs more help than this

TRANSFER, bed to chair and back:
3 needs no help
2 needs minor help, verbal or physical: Can transfer with one person easily, or needs supervision.
1 needs major help: two people or one strong/trained person, but can sit unaided.
0 cannot sit; needs skilled lift by two people (or hoist)

TOILET USE
2 able to get on and off toilet or commode, to undress and dress sufficiently, and to wipe self without physical or verbal help.
1 needs some help, can wipe self and do some of the rest with minimal help only.
0 needs more help than this.

MOBILITY around house or ward, indoors:
3 may use aid (stick or frame etc. but not wheelchair).
2 needs help of one person, verbal or physical, including help standing up.
1 independent in wheelchair, incl. able to negotiate doors and corners unaided.
0 needs more help than this.

STAIRS
2 independent up and down, and can carry any necessary walking aid
1 needs help, verbal or physical, or help carrying aid
0 unable

BATHING
1 able to get in and out of bath or shower, washes self without help (may use any aids)
0 unable.

APPENDIX II SIP 68 Questionnaire

Somatic autonomy

1. I get around in a wheelchair.
2. I get dressed only with someone's help.
3. I do not move into or out of bed by myself, but am moved by a person or mechanical aid.
4. I stand up only with someone's help.
5. I do not fasten my clothing, e.g., require assistance with buttons, zippers, shoelaces.
6. I do not walk at all.
7. I do not use stairs at all.
8. I make difficult moves with help, e.g., getting into or out of cars, bathtubs.
9. I do not bathe myself completely, e.g., require assistance with bathing.
10. I do not bathe myself at all, but am bathed by someone else.
11. I do not have control of my bladder.
12. I am very clumsy in body movements.
13. I do not have control of my bowels.
14. I feed myself with help from someone else.
15. I do not maintain balance.
16. I use a bedpan with assistance.
17. I am in a restricted position all the time.

Mobility control

1. I go up and down stairs more slowly, e.g., one step at a time, stopping often.
2. I walk shorter distances or stop to rest often.
3. I walk more slowly.
4. I use stairs only with mechanical support, e.g., handrail, cane crutches.
5. I walk by myself but with some difficulty, e.g., I limp, wobble, stumble, have a stiff leg.
6. I kneel, stoop, or bend down only by holding onto something.
7. I do not walk up or down hills.
8. I get in and out of bed or chairs by grasping something for support or using a cane or walker.
9. I stand only for a short period of time.
10. I dress myself, but do so very slowly.
11. I have difficulty using with my hands, e.g., turning faucets, using kitchen gadgets, sewing, doing carpentry.
12. I move my hands or fingers with some limitation or difficulty.

Psychic autonomy and communication

1. I have difficulty reasoning and solving problems, for example, making plans, making decisions, learning new things.
2. I have difficulty doing activities involving concentration and thinking.
3. I react slowly to things that are said or done.
4. I make more mistakes than usual.
5. I do not keep my attention on any activity for long.
6. I forget a lot, e.g., things that happened recently, where I put things, appointments.
7. I am confused and start several actions at a time.
8. I do not speak clearly when I am under stress.
9. I have difficulty speaking, e.g., I get stuck, stutter, stammer, slur my words.
10. I do not finish things I start.
11. I have trouble writing or typing.

Social behaviour

1. My sexual activity has decreased.
2. I am cutting down the length of visits with friends.
3. I am drinking fewer fluids.
4. I am doing fewer community activities.
5. I am doing fewer social activities with groups of people.
6. I am going out for entertainment less often.
7. I stay away from home only for brief periods of time.
8. I am eating much less than usual.
9. I am not doing heavy work around the house.
10. I do my hobbies and recreation for shorter periods of time.
11. I am doing less of the regular daily work around the house than I would usually do.
12. I am cutting down on some of my usual inactive recreation and pastimes, e.g., watching TV, playing cards, reading.

Emotional stability

1. I often act irritable toward those around me, e.g., I snap at people, give sharp answers, criticize easily.
2. I act disagreeable to family members, e.g., I act spiteful, I am stubborn.
3. I have frequent outbursts of anger at family members, e.g., I strike at them, scream, throw things at them.
4. I act irritable and impatient with myself, e.g., I speak badly about myself, I swear at myself, I blame myself for things that happen.
5. I do not joke with family members as I usually do.
6. I talk less with those around

Mobility range

1. I am not doing any of the shopping that I would usually do.
2. I am not going into town.
3. I am not doing any of the house cleaning that I would usually do.
4. I am not doing any of the regular work around the house that I would usually do.
5. I stay home most of the time.
6. I am not doing any of the clothes washing that I would usually do.
7. I am not going out to visit people at all.
8. I am getting around only within one building.
9. I have given up taking care of personal or household business affairs, for example paying bills, banking, working on budget.
10. I do not get around in the dark or in unlit places without someone's help

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Chapter 6

General discussion: Rationing of renal replacement therapy in elderly patients with end-stage renal disease

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Submitted for publication

Rationing of renal replacement therapy in elderly patients with end-stage disease

In the early years of the last century the first experiments with an artificial kidney were performed in animals. Although in the nineteen fourties some humans received dialysis, maintenance dialysis became only available in 1960 with the development of the vascular dialysis canula.[1]
In the Netherlands nowadays, dialysis care is provided in 48 dialysis centers. Most of these centers offer peritoneal dialysis and hemodialysis. Between 1985 and 1995 the number of patients receiving dialysis almost doubled to nearly 4000, and it has been growing since. Each year more than 1300 patients start dialysis treatment.[2]
Recent Dutch data (RENINE) indicate that on 1 January 1998 6437 patients were treated with some form of renal function replacement therapy (40.7 per 10^5 inhabitants). Distribution of the different treatment modalities was: 2322 (36%) passive centre hemodialysis, 847 (13%) CAPD, 93 (1.5%) home dialysis and 3175 (49.5%) had a functioning renal transplant.
Despite 450 renal transplantations there was an increase in the number of patients for a dialysis treatment.
Dialysis technology has been improved the last decade, nevertheless annual mortality of dialysis patients has increased from 13 to 21% over the same period. This increasing mortality rate is seen worldwide and according to many investigators this is due to an increasing number of elderly patients and patients with more comorbidity.
Especially in elderly patients renal failure is a serious condition with a high morbidity and still a bad prognosis quo ad vitam. In elderly patients, treated with RRT, survival is limited in comparison with younger patients. Renal transplantation is still limited mostly to the young patient with end-stage renal disease due to a scarcity of donor kidney's, resulting in a continuous rise of the mean age in the dialysis facilities. On 1 January 1992 over 40% of the dialysis patients were 65 years of age or over. Dialysis treatment is no treatment for renal failure, but is a life sustaining technique. Treatment decisions concerning dialysis therefore are decisions concerning life and death.
From the moment of introduction of maintenance dialysis only a percentage of patients who could have potentially survived were actually treated. Even in the United States of America with its, from our point of view, almost unlimited resources, dialysis treatment is widely but not unlimited available. Budget limitations, but also scarcity in machines and staff, make the necessity of patient selection still unavoidable.
Despite the fact that selection has always been an item in dialysis treatment, a general concept how to perform this selection is never been developed. Local institutions each designed its own method of deciding and when these methods were revealed they received much, and often adverse, publicity.[3,4]
National governments have often undertaken measures to facilitate general accessibility of dialysis. However there are also examples of national restrictions

for this kind of life saving treatments. The most striking example is of course the United Kingdom where resources were and still are restricted by financial constraints.
Sociological or medical criteria are often used in selection decisions. The age criterion is probably most widely used, with the intention to screen out the very young and the oldest patients. In dialysis the age criterion has been employed during the seventies and eighties of the last century.[5] In the Netherlands, aged-based decisions on dialysis remained in operation until the mid eighties. In heart transplantation still many centers accept only candidates who are less then 55 years of age. Often is stated that an age criterion is legitimate because it screens out elderly patients, who are in no physical condition to benefit from treatment.[6] In this way age-criteria are used as some kind of medical-benefit criterion. From a more sociological point of view, the benefit that society will receive of the treatment of an elderly patient is probably less than of a young patient. Also an economic argument can be used to justify selection on basis of age. Modern medicine has accomplished compression of morbidity, meaning that many diseases become overt at the end of life. A large percentage of the medical costs are made for elderly patients. So when age is used to screen out patients a considerable amount of money can be saved.
In many ways an age criterion seems to be an objective criterion. However objectivity does not necessarily makes a criterion appropriate. Elderly patients may well be the weakest group of patients and thereby a.vulnerable group, who might be easily excluded. However this should be a reason for special care instead of less care. In this respect the term intergenerational solidarity is often used indicating that a caring society should provide the same kind of attention to the elderly (and the very young) as is given to economically active part of the population.[7]
Nevertheless for dialysis some kind of selection or better perhaps rationing will be necessary. A definition of rationing could be a clear and direct limitation on individual access to a scarce good or service according to some categorical criteria other than the market.[7] These criteria should be preferably not political but medical, evidence based, criteria.

Our data show that in the Netherlands rationing is not altogether clear and overt. Although most nephrologists do not consider age as a selection criterion, we found in our study less patients from the eldest age group in the treatment population. Treatment is more often offered to younger patients than to older patients, resulting in a significant difference in the mean age between treated and untreated groups.[8] Whether the general physician also plays a role in this phenomena remains unclear. Besides this ageism there is also a trend of sexism. In our studies we find an overrepresentation of male patients. In the literature however, we also do find this male preponderance.[9] End-stage renal disease has to be considered as – a late – manifestation of atherosclerotic disease. This explains probably why men are more often seen at the nephrology department. Women, with a later onset of atherosclerotic disease, often do not reach this late stage of vascular impairment because they die from other causes.

From our findings, it appears that other factors that favour treatment include a high serum creatinine (indicating a severe renal impairment), the causative diagnosis of glomerulonephritis and/or nephrosclerosis, lower body mass, a low Charlson index (indicating less comorbidity), and the presence of a partner.

We did found in our retrospective survey a mean survival time of 463.2 days for elderly patients treated with RRT vs. 323.4 days for patients who did not receive RRT. In the age group 65-70 mean survival was 484.7 days (median survival 397 days). Patients aged 71-75 had a mean survival of 468.5 days (median 273 days). In the age group 75-80 mean survival was 328.2 days with a median survival of 28.5 days. In the age group over 80, mean survival was 192.9 days with a median survival of 32 days.
In all but the highest age group mean and median survival was better in the patients who underwent RRT in comparison to the patients who did not receive renal replacement therapy. In patients over the age of 80 years, mean survival was better in the group not treated patients. Treatment did give in this age group only a slightly better median survival.[10] Given these results there are few arguments to offer RRT to patients over 80 years of age. In this age group only strong individual arguments can be a reason to offer RRT.

The diagnoses cardiac disease, diabetes mellitus type II, and postrenal causes of renal disease negatively influenced survival. The latter probably because the high incidence of a malignancy of the prostate as a cause for postrenal obstruction. The diagnosis glomerulonephritis was, in our population, strongly associated with a longer survival.
In each age group, the influence of comorbidity was apparent. Survival was shorter within each age class when a higher Charlson score was present. This is in accordance with literature. A Charlson index of 0 is correlated with a one-year survival of 88%, an index of 1-2 with a one-year survival of 74%; an index of 4-5 and •5 are respectively correlated with a one-year survival of 48 and 15%.[11] (Figure 6.1) Cardiovascular disease, diabetes mellitus malignancies and diabetic organ damage are all represented in the Charlson index. In our data these conditions are associated with a shorter survival. Therefore it seems reasonable to reconsider RRT in patients with a Charlson index of >2.

Problems with urine production and continence are considered to be an expression of the poor condition of the patient These findings are in line with the finding that urinary incontinence is associated with a poor prognosis of elderly in-hospital patients.[12]
Acute onset of ESRD in the elderly was accompanied by an increased mortality in our study population. Especially the elderly patients who reach the criteria for end-stage renal disease within two weeks, acute renal failure, have a bad prognosis.[10] In these patients there is a rapidly progressive disease with a very serious impact on the patient. A longer and more gradual onset of renal failure, with the possibility of a timely onset of treatment, was characterized by a better patient survival. However, a long renal history of more than 5 years, before treatment was started shows an increase in the number of patients dying during

the follow-up period. This phenomenon is seen in male as well female patients. This emphasizes once more that the moment RRT is started is very crucial in elderly patients.

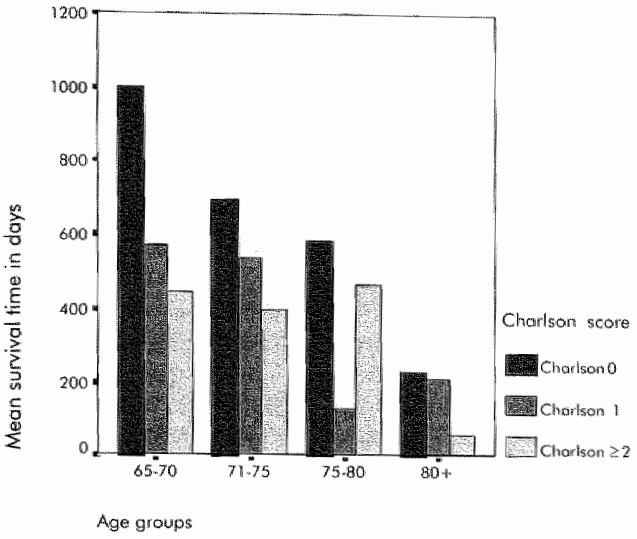

Figure 6.1 Survival in relation to Charlson index

Dialysis patients perform worse on mobility and ADL-ability than older control patients.[13] Consequently they are in need of more informal and professional help than the control patients and even then the pre-dialysis patients. Especially in male patients, disease lays a heavy burden on the partner. In our data we find more patients living with a partner on RRT in comparison to patients on RRT. Also we find in this group more patients with care provided by the children. Most likely this is due to selection meaning that patients with a solid social basis are more often accepted for RRT. This so-called supportive environment criterion was in use in the past in the United States for entering dialysis treatment before federal funding brought renal replacement therapy in reach for a larger number of patients.[14] Sometimes even marital status was used as entry criterion.[15] This criterion is however difficult to apply. There is no general consensus on exactly what environmental factors facilitate effective treatment. Little or no evidence from studies is available on the relation of environment and medical benefit. The patient himself cannot be held responsible for his poor environmental conditions. However one has to realise that renal replacement therapy in elderly patients in general, and especially in elderly patients with insufficient support imposes high demands on the dialysis facility. In this respect we want to make strong recommendations that a dialysis facility takes special measurements to assure that a patient never is rejected because lack of supportive care.
In a logistic regression model using a stepwise backward strategy, we found serum creatinine, the diagnosis of glomerulonephritis, and the need for a urinary catheter as independent factors that favoured treatment.[10] In our follow-

up study we found no relation between the value of serum creatinine and the success of the treatment. It is conceivable that doctors are impressed by a very high serum creatinine, but this number alone cannot be used as a factor in decision making. The causative diagnosis glomerulonephritis is associated with a relatively good prognosis in patients with end-stage renal disease treated with renal replacement therapy. Most likely is this the result of the fact that these patients have less atherosclerotic lesions in comparison with elderly patients. So in elderly patients with glomerulonephritis RRT should be strongly recommended.
We hardly encountered patients with cognitive deterioration or overt dementia in our study population. Without doubt this is due to selection. Is it reasonable to exclude patients with cognitive impairment from an intensive treatment as RRT? In this respect the scores on the sickness impact profile we found in dialysis patients are very important.[13] Scores of pre-dialysis patients resemble scores of elderly patients without renal disease, where patients stable on RRT had significantly higher scores. Functional observations give no indication of more depressive feelings in RRT patients. A possible cause may be a feeling of no longer being in control when on renal replacement therapy. In favour for this explanation is the relative high score of dialysis patients on the item social behaviour in the SIP68. Also higher scores on mobility control and somatic autonomy can point in this direction. This finding is in sharp contrast with the general feeling that renal replacement therapy is not only prolonging life but also is improving quality of life. This aspect of renal replacement therapy should be thoroughly discussed with a patient before starting RRT. It is our feeling that consent by proxy is not enough to impose a therapy with such an intensity on a patient, but that the decision to undergo this therapy should be made by a patient capable to assess the weight of this decision. So, in our opinion, a major impairment of the cognitive function will make the patient not suitable for RRT.
It is possible that patients on CAPD have a better appreciation of the quality of their life. The mean total SIP68 score is suggestive in this way. But here cognitive impairment will make this kind of renal function replacement therapy impossible because of the technical demands this therapy imposes on the patient.
In general can be said that following literature CAPD is better endured by elderly patients and a greater effort should be made in the Netherlands to include more elderly patients in CAPD programs.

Based on our findings it is possible to draw an algorithm for decision making in elderly patients with end-stage renal disease (Figure 6.2). It should be noted that this algorithm is based on retrospective and cross-sectional studies and is not tested in a prospective investigation.
Furthermore the assumption is made that this kind of algorithm is applied in an institution with ample resources for supportive care for elderly patients on RRT and also equipped to offer palliative care for patients with ESRD not on RRT.
Finally we want to emphasize that this algorithm can be only a helpful tool in decision making and never can or will replace the judgement of a skilful doctor who reaches consensus with his or her patient.

So, in an elderly patient with ESRD and in need of RRT, the first issue which must be answered is whether the patient is able to understand the information given to him by his doctor and to reach a decision.
Renal replacement therapy should be offered to a patient under 80 years of age when the causative diagnosis is glomerulonephritis and/or when mild comorbidity is present (Charlson index 2 or under). A more severe comorbidity or a bad score on the Barthel index (<15 but >5) should raise serious questions whether RRT is appropriate for the patient. However, individual arguments can be in favour for a treatment decision. In our opinion no RRT should be offered to patients 65-80 years of age in the presence of a high comorbidity score and a bad performance on the Barthel index.
In patients over 80 years of age RRT is not leading to a better survival. RRT therefore can be offered to patients who are in a very good condition (high scores on the Barthel index and no serious comorbidity), especially when the causative diagnosis is glomerulonephritis.

The better appearance of the pre-dialysis patients is a possible disadvantage for this group of patients. In spite of their better performance on mobility and ADL-tests and also on the SIP68, their mean survival, when started on RRT is shorter than that of patients stable on dialysis. In this way these patients confront us with a dilemma. They are feeling better and performing better when not on RRT. On the other hand when started on dialysis they have a mean survival of a little more than one year. During this period as we found the feeling of well-being is diminished. An earlier start of RRT therefore will probably prolong life but at a high price since a loss of the feeling of well-being seems to be associated with RRT.

One must bear in mind that we studied a selected population. It is widely known that elderly patients with ESRD are often not referred to the hospital by the general physician. This phenomenon probably influenced the finding that an acute deterioration of renal function in our population was most often seen in the eldest age group. A slow and gradual loss of renal function in this group is probably accepted as a hallmark of the end of life and does not usually lead to referral. However, survival appears to be influenced by renal history. Patients with a long renal history and, consequently, a more gradual and less aggressive progression of the renal disease, are probably more suited candidates for RRT (Figure 6.1.). It may be concluded that the "wrong" category of elderly patients is usually referred to the hospital, especially in the eldest age group. In future we should try to achieve a situation where elderly patients with a deterioration of their renal function are referred to a specialized institution. Here not only the cause of the renal impairment should be carefully diagnosed, but also should be investigated whether the patient is eligible for RRT, also and propably most important, the right moment to start RRT should be determined.

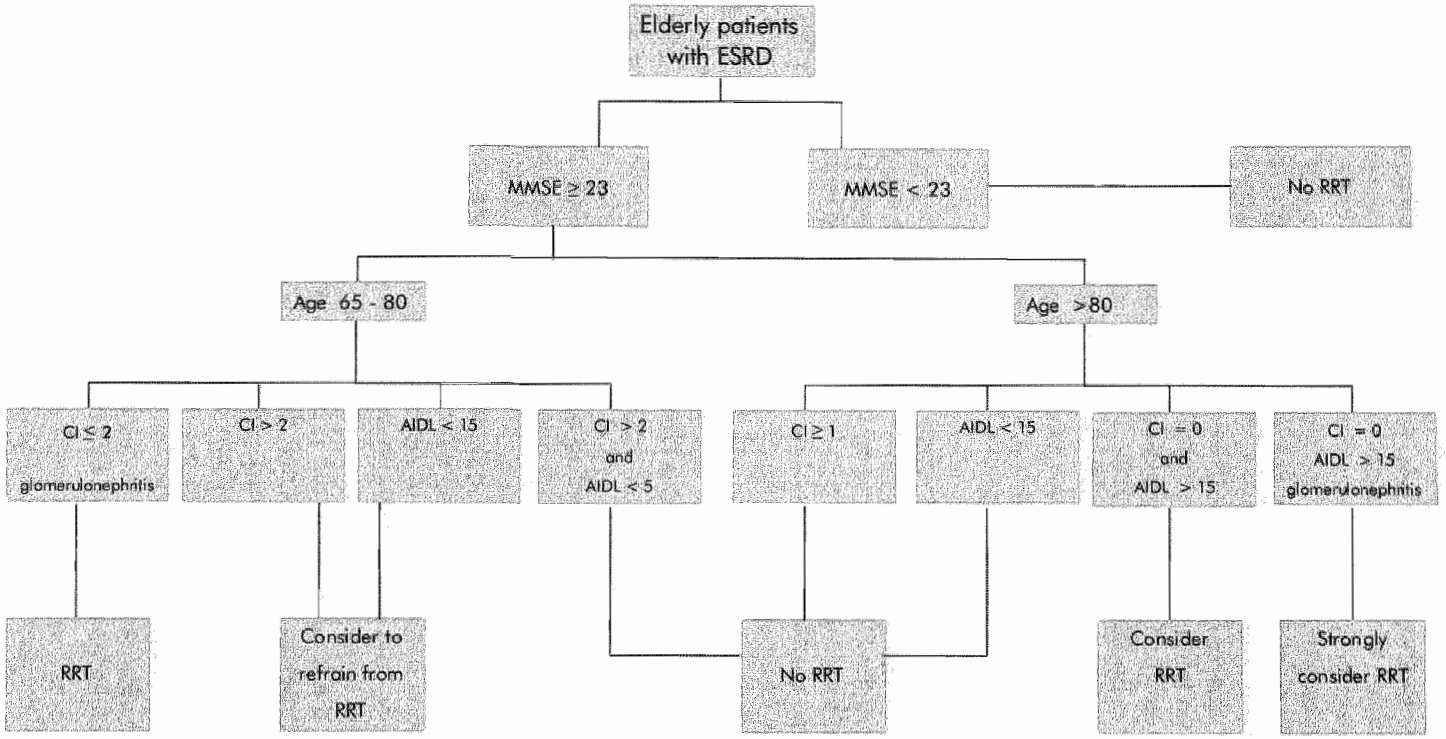

Figure 6.2 Descision algorithm in elderly patients with end-stage renal disease.
MMSE = Mini Mental State Examination; CI = Charlson Index for comorbidity; AIDL = Barthel Index for instrumental activities of daily living.

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Chapter 7

Summary

Summary

The topic of this thesis is end-stage renal disease (ESRD) in elderly patients. Due to both patient-related factors and ever-increasing health care expenditures, some kind of selection of elderly patients for renal replacement therapy (RRT) is inevitable. The aim of the studies we undertook was to design a simple algorithm to assist doctors in making treatment decisions and to help them find the best possible match between patients and therapy. In this way, not only can renal replacement therapy be offered to patients who will benefit the most from this treatment, but patients less suited for this procedure can also be spared much suffering.

In chapter 1, a short outline of this thesis is given.

Chapter 2 reviews the literature on renal function and renal disease in elderly people (chapter 2A), as well as on renal replacement therapy (RRT) and renal transplantation in elderly patients (chapter 2B).

In chapter 3 the results are presented of a retrospective survey among 331 elderly patients (65-95 years of age) with end-stage renal disease in four hospitals with a dialysis facility in the south-eastern part of the Netherlands. Of interest were the incidence of renal failure in the elderly population, clinical characteristics of these patients, and the accessibility of RRT programs for elderly patients. When including both patients undergoing RRT and patients with ESRD (yet) on RRT, the incidence of renal failure 2.2 per 1000 elderly inhabitants, which is higher than that usually reported in the literature. Hypertension, renal vascular disease, cardiac failure, diabetes mellitus, and post-renal obstruction were the most frequently encountered diseases leading to ESRD in these elderly patients. An extensive comorbidity was found in this population. The comorbidity was classified using the Charlson index, a score based on 19 diseases. The relative risk of death within 1 year after clinical admission for one of these diseases determines the score. A Charlson Index of 1 was found in nearly 30% of the patients, and a Charlson Index of 2 or more in 16%.
135 patients (41%) enrolled in a RRT program, mostly passive center hemodialysis. Seventy of these patients (52%) died within the 2-year inclusion period. Age and renal diagnosis proved to be important factors for entering RRT. Most patients entering RRT were from the youngest age group (65-70 years). In the higher age groups acute RRT was more common than in the lower age groups.
Of the 196 patients not treated with RRT, 112 (57%) died within the observation period. This survey did not clearly reveal which factors were taken into account in the treatment decision.

In chapter 4, 274 patients are studied who developed ESRD between 1 January 1992 and 31 December 1993. Patients who were admitted to a RRT program,

as well as those who were not undergoing renal replacement therapy, were studied. A follow-up of these patients was carried out until 31 December 1999. Of these patients, 96 were enrolled in RRT programs and 178 patients were not. Logistic analysis showed that selection for treatment was significantly associated with serum creatinine and the causative diagnosis glomerulonephritis. Cardiac and postrenal causes of ESRD as well as incontinence for urine were associated with a smaller chance of being admitted to a RRT program. Mean survival was calculated of the patients who died. In those patients who underwent RRT aged 65-70, survival was 570 days; in those aged 71-75, it was 641 days; in patients 76-80 years of age survival was 351 days, and in those over 80 years of age it was 102 days. In the group that did not receive RRT, mean survival was also calculated for patients who died. In patients aged 65-70, 71-75, 76-80, and over 80 years, survival was 418, 370, 322, and 221 days, respectively. Survival was dependent on age and comorbidity. Acute onset of ESRD in the elderly was accompanied by an increased mortality, where a more gradual onset was characterized by a better patient survival. Furthermore, comorbidity was of importance in patient survival.

In chapter 5, the effect of RRT on well-being and the quality of life of elderly patients is studied. Elderly patients are often in poor physical condition before the initiation of dialysis treatment. The most common symptoms are anorexia, weight loss, generalized weakness, encephalopathy, nausea, and vomiting. RRT often results in an improvement in their physical condition. We hypothesized that poor physical condition before the initiation of RRT would be reflected in high scores on a sickness impact scale. Improvement in physical condition by being stable on RRT would, in that case, lead to lower scores on the sickness impact profile. Therefore, we compared 16 elderly ESRD patients, selected for, but not yet on, RRT with 107 elderly patients stable on RRT. To assess the degree of improvement in quality of life, we also included 59 consecutive patients, referred to the outpatient facility of the geriatric department, in the comparison. Patients on dialysis scored lower on mobility and ability to perform daily activities (ADL) than pre-dialysis and control patients. The impact of ESRD on elderly pre-dialysis patients was deterioration in their functional capability over a period of 3 months. Nevertheless, the sickness impact profile, measured by the SIP-68, showed patients stable on RRT as having the highest scores. Thus, in this patient category, improvement in physical condition does not lead to improvement in the feeling of well-being. No signs of depression could be found in these patients. Therefore we speculated that their feeling of no longer being 'in control' was the cause for their high scores on the sickness impact profile of elderly RRT patients.

In chapter 6 we propose a simple algorithm for rationing RRT in elderly patients. In this algorithm, an important item is the cognitive functionality of the patient. RRT has a major impact on the elderly patient. It probably improves his or her physical condition and, in patients under 80 years of age, leading to a better survival. On the other hand, RRT does not improve the feeling of well-being and leads to higher scores on the sickness impact profile. Each patient

must have the right to make his or her decision in this matter. Good and ample information from the doctor, as well as the ability to understand this information and make an independent choice, are essential in this respect. In patients with a severe cognitive impairment, RRT should not be considered because the patient is not able to participate in the decision making.
Comorbidity, ADL-ability and the causative diagnosis of ESRD are factors that are also important in making the decision to initiate RRT. In patients aged 65-80 with no overt cognitive impairment, mild comorbidity, good ADL-ability and the causative diagnosis of glomerulonephritis should be encouraged to start RRT. In contrast patients with extensive comorbidity and a poor ADL-ability should not be encouraged to dose. In patients with intermediate scores on ADL and comorbidity, a more individual approach must be taken before a treatment decision can be made.
In patients over the age of 80, survival is highly determined by the age. Survival is not better in patients treated by RRT, than in those not treated by RRT. RRT should only be considered when there is no comorbidity and very good ADL-ability. Again, the causative diagnosis of glomerulonephritis favours treatment in these patients.

Chapter 8

Samenvatting

Samenvatting

Dit proefschrift handelt over terminale nierinsufficiëntie bij ouderen. Hiervoor is nierfunctie vervangende therapie (nierdialyse) nodig. Dit is een voor de patiënt zware behandeling waarvoor hij of zij, meestal meerdere malen per week, naar het ziekenhuis moet komen. Daarnaast is het ook een zeer kostbare behandeling. Het aantal ouderen met eindstadium nierfalen neemt de laatste jaren sterk toe als gevolg van de toename van atherosclerotisch vaatlijden. Deze toename, gevoegd bij het feit dat er een beperkte ruimte is op de dialyse afdeling, maakt het noodzakelijk die patiënten te selecteren die het meeste baat hebben bij en het beste bestand zijn tegen het ondergaan van deze hightech behandeling.
Het doel van het onderzoek beschreven in dit proefschrift is dan ook een simpele beslisboom op te stellen die dokters kunnen gebruiken om op een objectieve manier te bepalen welke oudere patiënt met eindstadium nierfalen in aanmerking moet komen voor nierfunctie vervangende therapie.

In hoofdstuk 1 wordt een beschrijving gegeven van de opzet van dit proefschrift en de onderzochte patiëntenpopulaties.

In hoofdstuk 2A wordt een overzicht gegeven van de internationale literatuur over de werking van de nier bij ouderen en welke nierziekten bij ouderen voorkomen. In hoofdstuk 2B wordt de literatuur besproken betreffende de behandeling van nierziekten bij ouderen.

In hoofdstuk 3 beschrijven wij de klinische kenmerken van oudere patiënten met eindstadium nierziekte op basis van een retrospectief onderzoek van 331 patiënten. Deze patiënten werden opgespoord via de geautomatiseerde laboratoriumbestanden van vier Limburgse ziekenhuizen, het Laurentius ziekenhuis in Roermond, het Maaslandziekenhuis in Sittard, het Atrium ziekenhuis in Heerlen en het academisch ziekenhuis te Maastricht. Er werd gezocht naar patiënten van 65 jaar en ouder met een serum creatinine van $\geq$400 μmol/l in de jaren 1992 en 1993. Op deze wijze konden wij niet alleen de patiënten die behandeld werden opsporen, maar ook die patiënten vinden die niet voor hun terminale nierziekte behandeld waren met dialyse. Dit maakte het mogelijk een uitspraak te doen over het voorkomen van eindstadium nierziekte bij ouderen. Onze schatting hiervan, een jaarlijks optreden van eindstadium nierziekte bij 2,2 ouderen per 1000 oudere inwoners, viel hoger uit dan de schattingen in de literatuur omdat wij ook de niet behandelde patiënten konden meetellen. Van de in totaal 567 patiënten die aan de criteria voldeden, kon van 331 patiënten een medisch dossier gevonden worden. Uit deze dossiers werden gegevens verzameld betreffende de klinische toestand, de oorzaak van de nierziekte, het tegelijkertijd voorkomen van andere ziektes en het percentage patiënten dat dialyse onderging. Hypertensie, vaatafwijkingen van de nieren, hartfalen, suikerziekte en obstructie van de urinewegen waren de meest

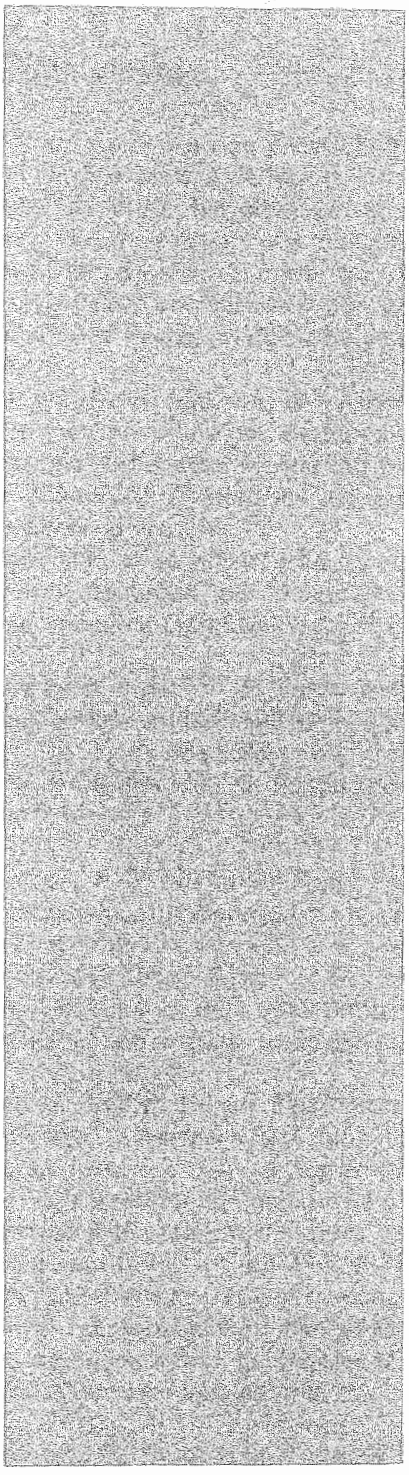
voorkomende oorzaken van nierfalen bij ouderen. De bijkomende ziekten, de co-morbiditeit, werd uitgedrukt in de Charlson index. Dit scoringssysteem kent een getal toe aan negentien veel voorkomende aandoeningen. Het relatieve risico op overlijden binnen één jaar na een klinische opname voor deze ziektebeelden bepaalt de hoogte van de score. Wij vonden een Charlson index van 1 bij ongeveer 30% van de patiënten en een index van 2 of meer bij 16%.
Met nierdialyse werden 135 patiënten (41%) behandeld. Hiervan overleden er 70 (52%) gedurende de inclusieperiode van twee jaar. De leeftijd en de diagnose betreffende de nierziekte bleken belangrijke factoren voor het al dan niet ondergaan van dialyse. De meeste patiënten die werden opgenomen in een nierfunctie vervangend programma kwamen uit de jongste leeftijdsgroep. Bij patiënten uit de hogere leeftijdsgroepen kwam vaker acute dialyse behandeling voor dan bij de jongere patiënten. Van de 196 patiënten die niet behandeld werden met dialyse overleden er 112 (57%) in de inclusieperiode van twee jaar.
Uit de medische dossiers kwam niet duidelijk naar voren welke criteria werden gebruikt om te beslissen of een patiënt wel of niet behandeld werd.

Voor het onderzoek beschreven in hoofdstuk 4 werd in principe dezelfde populatie gebruikt als die in hoofdstuk 3. Alleen werden nu de patiënten bestudeerd die in de inclusie periode hun nierfalen ontwikkelden. Het klinisch beloop bij deze patiënten werd vervolgd tot 31 december 1999. Van deze 274 patiënten werden er 96 behandeld met nierdialyse en 178 patiënten ondergingen geen nierfunctie vervangende therapie. Logistische regressie analyse toonde aan dat selectie voor dialyse was geassocieerd met de hoogte van het serum creatinine en de diagnose glomerulonefritis. Wanneer de oorzaak van het nierfalen een hartaandoening was of lag in obstructie van de urinewegen, was de kans op behandeling kleiner, evenals bij patiënten die incontinent waren voor urine.
Van de patiënten die overleden tijdens de follow-up kon de gemiddelde overleving berekend worden. Voor de dialyse patiënten bedroeg deze gemiddelde overleving 570 dagen in de leeftijdsgroep 65-70 jaar. In de leeftijdsgroepen 71-75 jaar, 76-80 jaar en de groep ouder dan 80 jaar was de gemiddelde overleving van de overleden patiënten respectievelijk 641, 351 en 248 dagen.
Van de niet met dialyse behandelde patiënten die overleden tijdens de follow-up was de gemiddelde overleving per leeftijdscategorie: 418, 370, 317 en 222 dagen.
De overleving bleek afhankelijk te zijn van de leeftijd en de co-morbiditeit. Acuut optreden van nierfalen ging gepaard met een hogere mortaliteit dan wanneer er sprake was van een meer geleidelijke ontwikkeling van het nierfalen.

In hoofdstuk 5 is de invloed van dialyse behandeling op het gevoel van welbevinden en de kwaliteit van leven bij de oudere patiënt het onderwerp van onderzoek. Ouderen zijn vaak in een slechte lichamelijke conditie op het moment dat ze aan dialyse behandeling beginnen. Veelal hebben ze geen eetlust, zijn ze afgevallen en is er sprake van gegeneraliseerde spierzwakte, verwardheid, misselijkheid en braken. Behandeling met dialyse leidt vaak tot

een sterke verbetering van hun lichamelijke conditie. Wij veronderstelden dat deze lichamelijke verbetering vergezeld zou gaan door een verbetering van gevoelens van welbevinden en lagere scores op een schaal van sickness impact. Om deze hypothese te bewijzen vergeleken wij 16 oudere patiënten vlak voor hun eerste dialyse behandeling met 107 patiënten die al langere tijd gedialyseerd werden en stabiel waren. Om de mate van verbetering te kunnen inschatten betrokken wij ook 59 patiënten zonder nierziekte van de polikliniek geriatrie in de vergelijking. In tegenstelling tot wat wij verwachtten scoorden de dialyse patiënten lager wat betreft mobiliteit en het vermogen tot het verrichten van ADL handelingen dat de pre-dialyse patiënten en de controle patiënten. Het effect van eindstadium nierziekte bleek bij de pre-dialyse patiënten uit een relatief laag lichaamsgewicht. Daarbij bleek hun functionele capaciteit in een periode van drie maanden achteruit te gaan. De scores op het sickness impact profile, de SIP68 waren het hoogst bij de dialyse patiënten. Deze patiënten scoorden laag op een depressie schaal. Op basis van deze bevindingen postuleren wij dat dialyse patiënten zich 'ziek' voelen omdat ze niet langer de controle over hun leven in handen hebben, maar afhankelijk zijn van een chronische en intensieve behandeling.

In hoofdstuk 6 wordt een relatief simpele beslisboom voorgesteld voor het toewijzen van dialyse behandeling aan oudere patiënten. In deze beslisboom is cognitieve functionaliteit een belangrijk item. Dialyse behandeling is een zware behandeling met belangrijke consequenties voor de patiënt. De patiënt heeft het recht hierin zijn eigen beslissing te nemen. Voorwaarde hiervoor is dat hij voldoende en volledig wordt geïnformeerd door zijn behandelende arts en hij in staat is deze informatie te begrijpen, om onafhankelijk een beslissing te nemen. Bij patiënten met cognitieve functiestoornissen moet een dialyse behandeling niet gestart worden wanneer ze niet voldoende in staat zijn in de besluitvorming te participeren.
Bij oudere patiënten in de leeftijd 65 tot 80 jaar zijn vervolgens een beperkte co-morbiditeit, een goede ADL functionaliteit en de diagnose glomerulonefritis, argumenten om te beslissen tot nierfunctie vervangende therapie. Bij patiënten in deze leeftijdscategorie met ernstige co-morbiditeit en/of slechte ADL functionaliteit zou afgezien moeten worden van dialyse. Wanneer er sprake is van een minder ernstige co-morbiditeit en matige scores wat betreft de ADL functies zal een meer individuele benadering van de patiënt uiteindelijk moeten leiden tot een beslissing over de behandeling.
Bij patiënten ouder dan 80 jaar wordt de overleving in hoge mate bepaald door de leeftijd. Dialyse verlengt de levensverwachting niet. Nierfunctie vervangende therapie moet alleen bij die patiënten overwogen worden wanneer er geen noemenswaardige co-morbiditeit aanwezig is en een vlekkeloze ADL functionaliteit. Ook de aanwezigheid van de diagnose glomerulonefritis is een argument voor behandeling.



Dankwoord

Dankwoord

Het schrijven van een proefschrift is een enorm karwei. Opvallend vaak wordt het vergeleken met de fysieke inspanningen die nodig zijn voor het bouwen van een huis. Nu ik het afgelopen jaar zowel het grootste deel van dit boekje heb geschreven en tevens ons huis grondig heb verbouwd kan ik uit eigen ervaring meedelen dat één en ander weinig met elkaar te maken heeft. Wel kan gesteld worden dat "bouwvakken" een goede afleiding is van "schrijven" maar dat je tijdens het werken in de bouw innig kan verlangen naar het rustig achter de PC zitten.
De enige overeenkomst is wellicht dat je tijdens beide werkzaamheden mensen ontmoet met een eigen deskundigheid die enthousiast kunnen praten over hun vak. Zowel het schrijven als het verbouwen geeft een unieke kans deze mensen te ontmoeten en met hen samen te werken en dat heb ik als buitengewoon inspirerend ervaren.
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Allereerst moet in dit verband genoemd worden Prof.dr. J.A. Flendrig. Hij schetste op een half a-4 tje de eerste opzet van dit proefschrift. Het is opvallend om te zien hoe dicht wij, zoveel jaren later, zijn uitgekomen bij zijn oorspronkelijk idee. Ik betreur het zeer dat hij hiervan geen getuige meer kan zijn.

Prof.dr. A.C. Nieuwenhuijzen Kruseman. Beste Arie, jij hebt mij niet alleen gewezen op het belang van het doen van onderzoek binnen de academische setting, maar hebt ook een serieuze poging gedaan het starten van mijn onderzoek mogelijk te maken, door te proberen daar tijd voor vrij te maken. Hoewel het voor mijn aanstelling bij het azM niet ongunstig was dat die poging mislukte, heb je zo de basis gelegd voor het onderzoek, waarvoor mijn dank.

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De beoordelingscommissie. Prof.dr. J.A. Knottnerus, Prof.dr. R.A.M.G. Donckerwolcke, Prof.dr. W.H.L. Hoefnagels. Prof.dr. R.Th. Krediet, Prof.dr. C. Spreeuwenberg. Ik dank u voor de zeer snelle en grondige beoordeling van het manuscript. Een aantal uwer nam daarbij nog de moeite om mij schriftelijk een aantal suggesties te doen om de lijn in het geheel duidelijker te maken. Sir Prof. J. Grimley Evans I would like to thank you for the many useful remarks you have send me after reading the draft version of this thesis.

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jullie kunnen constateren dat er in de 'periferie' hard gewerkt wordt bij gunstiger secundaire arbeidsomstandigheden.

Een aantal studenten hebben in een wetenschaps-stage een bijdrage geleverd aan het onderzoek; van hen noem ik hier Mascha Spee, Tim Jansen en Sascha de Gast. Ik heb veel plezier beleefd aan de samenwerking. Ik hoop dat het wederzijds geweest is.

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Curriculum vitae

Curriculum Vitae

De auteur van dit proefschrift werd geboren in Amsterdam. Na de lagere school, de school met de Bijbel 'Elout van Soeterwoude', behaalde hij het diploma gymnasium-ß aan het Christelijk Lyceum Zuid in Amsterdam. Uitgeloot voor de studie geneeskunde, studeerde hij aanvankelijk psychologie aan de subfaculteit psychologie van de Vrije Universiteit te Amsterdam. Aan dezelfde universiteit studeerde hij vervolgens Geneeskunde. Het artsexamen werd afgelegd in 1983. Na een korte periode als agnio werd de specialisatie interne geneeskunde begonnen in het ziekenhuis st. Joannes de Deo in Haarlem (opleider dr. J.A.P. de Fockert). De opleiding werd vervolgd vanaf 1985 in het Academisch Medisch Centrum, het Academisch ziekenhuis bij de Universiteit van Amsterdam (opleiders Prof.dr. A. van Leeuwen en Prof.dr. J. Vreeken). Op 1 augustus 1988 vond de registratie tot internist plaats. Vervolgens werd hij in het AMC aangesteld als specialist patiëntenzorg en was onder andere betrokken bij de ontwikkeling van een polikliniek voor vetstofwisselings-stoornissen in dit ziekenhuis.
In 1992 volgde de verhuizing naar Maastricht waar hij tijdelijk werd aangesteld als staflid bij de afdeling Interne Geneeskunde (Hoofd Prof.dr. J.A. Flendrig) in de werkgroep Algemeen Interne Geneeskunde. Binnen deze werkgroep is zijn aandachtsgebied de geriatrie.
In 1994 werd hij aangesteld als staflid in vaste dienst bij de afdeling Interne Geneeskunde (hoofd Prof.dr. A.C. Nieuwenhuijzen-Kruseman).
In 1985 is hij getrouwd met Astrid Spee. Zij hebben samen twee kinderen: Peter (1987) en Maarten (1989).