KIDNEY TRANSPLANTATION IN THE ELDERLY

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LIST OF PAPERS

1. Heldal K, Leivestad T, Hartmann A, Svendsen MV, Lien BH, Midtvedt K. Kidney transplantation in the elderly--the Norwegian experience. Nephrol Dial Transplant 2008 Mar;23(3):1026-31.

2. Heldal K, Hartmann A, Leivestad T, Svendsen MV, Foss A, Lien B, Midtvedt K. Clinical outcomes in elderly kidney transplant recipients are related to acute rejection episodes rather than pretransplant comorbidity. Transplantation 2009 Apr 15;87(7):1045-51.

3. Foss A, Heldal K, Scott H, Foss S, Leivestad T, Jorgensen PF, Scholz T, Midtvedt K. Kidneys from deceased donors more than 75 years perform acceptably after transplantation. Transplantation 2009 May 27;87(10):1437-41.

4. Heldal K, Hartmann A, Grootendorst DC, de Jager DJ, Leivestad T, Foss A, Midtvedt K. Benefit of kidney transplantation beyond 70 years of age. Nephrol Dial Transplant in press.

ABBREVIATIONS

AZA	azathioprine
CCI	Charlson comorbidity index
CKD	chronic kidney disease
CsA	cyclosporine A
CVD	cardiovascular disease
DM	diabetes mellitus
ECD	expanded criteria donor
ESP	Eurotransplant Senior Program
ESRD	end stage renal disease
HLA	human leukocyte antigen
HR	hazard ratio
HD	hemodialysis
IL-2R	interleukin 2 receptor
KDRI	Kidney Donor Risk Index
LYFT	Life Years From Transplant
MMF	mycophenolate mofetil
NHANES	National Health and Nutrition Examination Survey
RCT	randomized clinical trial
PD	peritoneal dialysis
RRT	renal replacement therapy

1. INTRODUCTION

1.1 Kidney transplantation

Since the first unsuccessful attempt in 1933 (1;2), kidney transplantation has progressed from being an experimental investigation to a safe and more or less routine clinical procedure. The first kidney transplantation to achieve a successful, long-term outcome was undertaken in Boston in 1954 by a team led by Dr. Joseph E Murray (3;4). A kidney was transplanted between two identical twins. Kidney function was restored and the recipient survived with good kidney function until suffering cardiac death eight years later. The donor suffered no serious side effects. Clearly, this success was of limited practical value since identical twins are rare. For his pioneer work with transplantation, Murray was awarded the Nobel Prize for medicine in 1990.

The success of the transplantation in 1954 inspired pioneering groups in Boston and Paris to perform unrelated transplantations using total body irradiation and corticosteroids as immunosuppression (5;6). This non-specific mode of immunosuppression was, however, both cumbersome and associated with serious side effects and unacceptable mortality rates from infections. In 1961, azathioprine (AZA) was introduced as an immunosuppressant for use in human organ transplantation (7;8). The immunosuppressive effect of AZA was reversible and could be achieved with a relatively low incidence of side effects. It now became possible to perform transplantations between individuals who were not genetically identical. Consequently, kidney transplantation became a viable treatment for selected patients with end stage renal disease (ESRD). At that time, graft survival at one year using AZA and steroids was approximately 50% (9).

Increased knowledge of the immunological mechanisms responsible for the development of rejection, and eventually the introduction of cyclosporine A (CsA) in 1982, resulted in further improvements in graft survival following kidney transplantation (10). Since then, new and more potent immunosuppressive drugs such as mycophenolate mofetil (MMF) and the interleukin 2 receptor (IL-2R) antagonists have been developed. The use of these drugs has led to even further reductions in acute rejection rates (11). These advances have made it possible to start large scale transplantation programmes and today kidney transplantation is the preferred treatment option in patients with ESRD eligible for the surgical procedure (12).

In Scandinavia, the first kidney transplantation was attempted at Rikshospitalet in Oslo, Norway in 1956. The first transplantation in Scandinavia to achieve a successful long-term outcome, however, was performed at Ullevål hospital in 1963. The recipient survived for 22 years before dying from a ruptured aortic aneurysm (13). Since 1983, as part of a national policy, all solid organ transplantations in Norway have been performed at Rikshospitalet. The number of kidney transplantations conducted at Rikshospitalet has steadily increased and now totals between 250 and 300 procedures per year.

1.2 Ageing population

The average age of the Norwegian population has increased markedly over the last three decades. The number of Norwegians aged 70 years or older has increased from 320,000 (8% of the total population) in 1970 to more than 500,000 (11% of the total population) in 2008. Based on a conservative estimate, this figure is likely to rise to approximately 840,000 (14% of the total population) by 2030 (14).

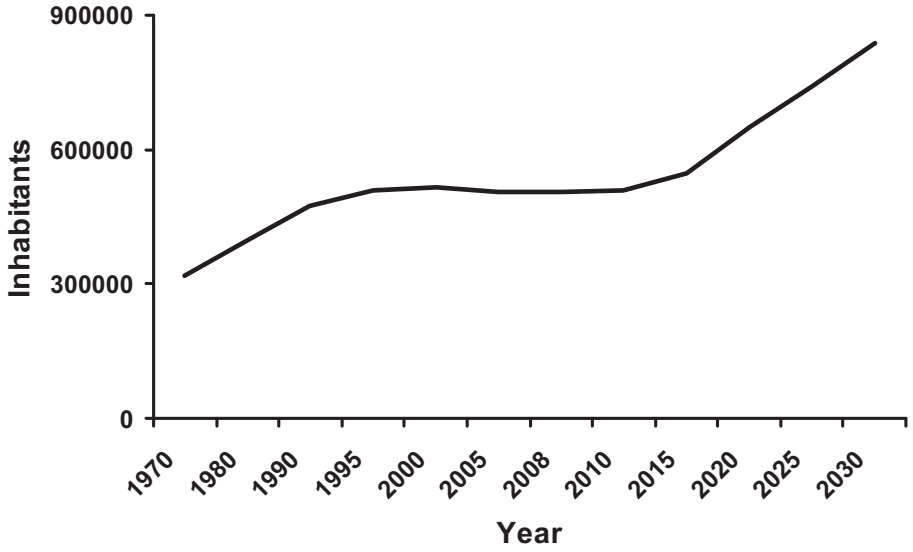

Figure 1. The Norwegian population over 70 years of age; past, present and future. Data extracted from www.ssb.no November 2008.

Similar demographic changes are taking place across most of the western world. In the European Union, it is estimated that the proportion of people older than 65 will increase from 16.7% in 2005 to 28.4% by 2050 (15). Similarly, in the United States, the proportion of people older than 65 is expected to increase from 12.4% in 2005 to 21.6% by 2050 (16). The increase in the elderly population has consequently led to a rise in morbidity rates.

1.3 Epidemiology and treatment options for elderly ESRD patients

Common risk factors for chronic kidney disease (CKD) include hypertension, cardiovascular disease (CVD), diabetes mellitus (DM), family history of CKD, and older age. The National Health and Nutrition Examination Survey (NHANES) is a series of health examination surveys, begun in 1960, designed to monitor the health and nutritional status of

the non-institutionalized, general population in the United States. The most recent survey was conducted between 1999 and 2004 and included 14,632 people aged ≥20 years (17). Data from this NHANES showed that the risk of CKD in people aged over 60 was much higher (odds ratio 5.89), compared with those aged between 20 and 39 (18). Data from the Norwegian Renal Registry in 2008 showed that vascular/hypertensive disease was the number one underlying cause of CKD and accounted for 27% of all new patients starting renal replacement therapy (RRT) (19). In patients older than 70 starting RRT, this figure rises to 46% (personal information – Torbjørn Leivestad October 2009).

CKD is staged according to severity from stage 1 to stage 5. RRT is usually not started before the patient has reached stage 5. Many elderly patients with stage 4 CKD have slowly declining kidney function and die before reaching stage 5 (20). Despite this, elderly patients have been the fastest growing 'population' requiring RRT both in Europe and in the United States (21-25). In 1980, the median age of patients starting RRT in Norway was 53 years. This had increased to 65 years in 2008 (19).

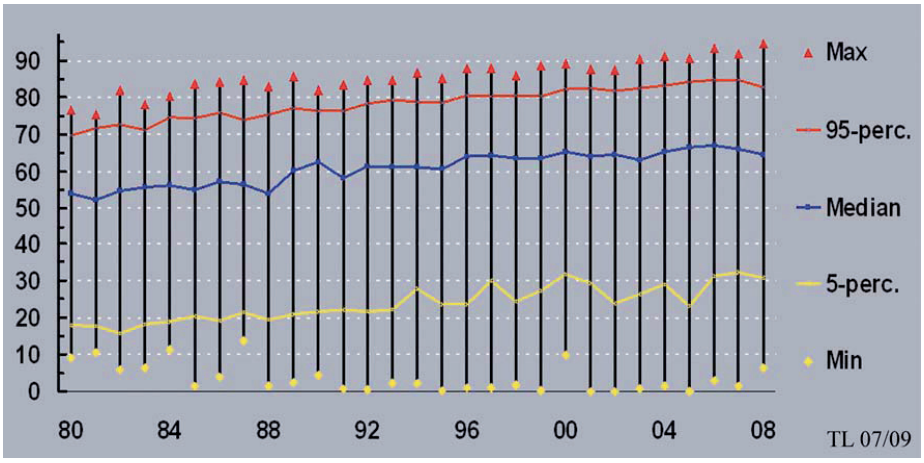

Figure 2. Age of new patients at start of RRT in Norway 1990 - 2008. Data retrieved from the Norwegian Renal Registry. Reprinted with permission from Torbjørn Leivestad.

As shown in Figure 2, the median age of patients starting RRT has stabilised during the last decade. Similar trends are observed in other countries (18;26). It is possible that the efforts made to prevent the development of ESRD, especially among patients with hypertension, have led to this stabilization. On the other hand, the absolute number of elderly patients in need of RRT will still increase substantially owing to the ageing populations described in section 1.2.

Patients with advanced CKD have different options for active treatment:

1. Dialysis, either as haemodialysis (HD) or peritoneal dialysis (PD).
2. Preemptive kidney transplantation.
3. Kidney transplantation after the start of dialysis.

Traditionally, elderly patients with advanced CKD have been selected for dialysis treatment, with only a small minority being considered for kidney transplantation. Elderly patients with severe comorbidity may be found unfit for active treatment although this may not lead to any shortening of their life expectancy (27). In some cases it is extremely difficult to decide whether a patient will tolerate, and thereby benefit from, dialysis treatment. Most elderly patients with advanced CKD develop symptoms that may either be suggestive of uraemia, or simply be a consequence of advanced age and/or comorbidity. In such cases it is sometimes necessary to start acute dialysis treatment in order to save the patient's life, and then decide subsequently if the treatment should be permanent or not. An important factor in this process is how long the patient is expected to survive, with or without active treatment. A recent report describing the outcome of 8,977 chronic dialysis patients showed that the mortality rate in patients with ESRD had not changed over the last 12 years, despite a significant increase in the age of the dialysis population (28). The authors' hypothesis is that selected patients benefit from the improvements in dialysis technology, uraemia

management, and treatment of dialysis-related complications. Interestingly, in patients aged over 74, the mortality rate significantly decreased during the 12 year observation period. Several strategies have been developed to predict early and long-term prognoses in CKD (29-31), and these may be used to help select patients eligible for RRT.

Kidney transplantation is generally regarded as the best treatment option for patients with ESRD (12;32-35). Previous studies indicate that selected elderly patients, despite having a limited life expectancy, often benefit from kidney transplantation (36-39). Consequently, the proportion of elderly patients on transplant waiting lists has increased during the last years. In 2008 in the United States, more than 15% of patients on transplant waiting lists were aged over 65 (40), compared with only 7% in 1997 (25). Similarly, in Europe, the proportion of kidney transplant recipients over the age of 65 has increased from 3.6% in 1991 to 19.7% in 2007 (41). The majority of previous reports concerning transplantation in 'elderly patients' have generally involved patients aged between 60 and 70 (36;42-46). There are few reports describing kidney transplantation outcomes in patients above 70 years old, and the most important of these publications are based on registry data from multiple centres reflecting various transplant protocols (24;38). Compared with age-matched dialysis patients, previous studies have indicated that survival and quality of life is favorable after transplantation even in recipients aged 65 - 70 (36;38;47-49).

1.4 Selection of elderly patients for kidney transplantation

The increasing number of elderly patients with ESRD presents great challenges for physicians. One such challenge is how to select which elderly patients with ESRD whom are most likely to benefit from kidney transplantation. Traditionally, a standard comorbidity

screening and treatment algorithm has been employed, independent of patient age. Patients with less comorbidity tend to be accepted for transplantation, while those with greater comorbidity receive life-long dialysis treatment.

In general, the degree of comorbidity, in particular diabetic nephropathy and cardiovascular disease, at the time of transplantation, has a deleterious effect both on recipient and allograft survival (50;51). There is, however, limited information available relating to the effects of comorbidity in kidney transplant recipients at an advanced age. Several scoring systems have been proposed to assess the burden of comorbidity at the time of kidney transplantation. The Charlson comorbidity index (CCI) has been validated as the best predictive tool for measuring comorbidity in this setting (52). The CCI score ranges from 0 (no comorbidity) to 24 (maximum comorbidity). The lowest possible CCI score at the time of kidney transplantation is 2 (the presence of pre-transplant kidney failure). The CCI score has been validated in patients older than 60 years (53), but it has not previously been evaluated as a prognostic index for mortality or graft loss in recipients older than 70 years.

1.5 Donor organ pool and allocation strategies

A major concern in kidney transplantation is the lack of organs. In general, there are far more patients on waiting lists than there are available organs. By March 31st 2008, 6,784 patients were waitlisted for a kidney transplant in the UK, whereas only 1,437 deceased donor and 829 living donor transplantations were performed the previous year (54). This inevitably means increased waiting times, and patients dying while on waiting lists. By the end of 2008, 10,687 patients were registered on the Eurotransplant kidney waiting list (55). Among these, 52% had been on the waiting list for more than two years, and 75% had been

on dialysis for more than two years. It would be difficult, even unethical, to expand the number of patients eligible for kidney transplantation, without simultaneously expanding the number of organs available. Strategies for expanding the overall donor pool include increased use of living donors (56-60), donation after cardiac death programs (61-65), altruistic living donation (66), introduction of standardized donor management protocols (67) and increased use of expanded criteria donors (ECD) (68-70). ECDs are defined as all deceased donors older than 60 years, and those aged 50 to 59 with at least two of three medical criteria: hypertension, cerebrovascular cause of death or serum creatinine level above 132.6 μmol/L (1.5 mg/dL) (56;71-73). An important issue in the allocation process is to match the suspected life of the transplant to the suspected life of the recipient. By avoiding giving young kidneys to elderly recipients it is possible to increase the overall graft life and thereby utilize the graft source as optimal as possible (74). Recently, a kidney donor risk index (KDRI) has been developed for estimating the risk of graft failure after transplantation (75). The Eurotransplant Senior Program (ESP) was launched in 1999 as an alternative old-for-old organ allocation system (76), and in the United States, a new allocation system named Life Years From Transplant (LYFT) is being considered (77).

1.6 The Norwegian experience with elderly kidney transplant recipients

The Norwegian kidney transplantation waiting list has, up to now, been kept relatively constant at below 50 per million inhabitants. This can be explained by a relative low incidence of ESRD (78) and an active living donor transplant programme (58;79), Patients have been accepted for kidney transplantation using a standard screening algorithm without a formal upper age limit. More than 20 years ago it was reported from our centre that transplantation was feasible even in selected patients beyond 70 years of age (80). Living

donations are also accepted, and in particular spousal donors are becoming increasingly common in this age group. Because we have one large transplant centre serving approximately 4.8 million inhabitants, and a liberal policy with kidney transplantation in elderly patients, we have, to our knowledge, the largest amount of data from a single centre describing kidney transplantation in the elderly.

2. AIMS OF THE STUDIES

The rising number of patients with ESRD placed on transplant waiting lists has led to the re-evaluation of selection criteria for transplantation, including in Norway. A common question is whether high age *per se* should be a contraindication for transplantation.

Primarily we wanted to evaluate outcomes in kidney transplant recipients older than 70 years and compare them with younger recipients, as well as identify clinical variables associated with good or poor outcome. We also wanted to compare outcomes of transplanted elderly patients with patients of the same age accepted for transplantation who had remained on dialysis while waiting for an appropriate organ. In addition, we also wanted to evaluate the use of older donors for older recipients.

We aimed to answer the following key specific questions:

1. **Is kidney transplantation a safe and preferred treatment for elderly ESRD patients without an upper age limit?**
2. **Are there any pre-transplant or early post-transplant modifiable clinical variables relevant to kidney transplantation outcomes in the elderly?**
3. **Should kidneys from old deceased donors be discarded owing to their advanced age?**
4. **Is kidney transplantation superior to dialysis in elderly patients with ESRD?**

3. SUBJECTS AND METHODS

3.1 Study design

3.1.1 Papers I - II

Survival data for all patients who received their first single kidney transplant at Rikshospitalet between 1990 and 2005 were retrieved from the Norwegian Renal Registry and analyzed as described in section 3.2.1. The patients were stratified according to their age at transplantation. The 'elderly' recipients, defined as those aged 70 years or older were compared with a group of 'senior' recipients aged 60 to 69 years old. These two groups were also compared with a control group consisting of 'average' adult kidney recipients at our centre (age 45-54 years).

Baseline clinical characteristics of the recipients were retrieved from the registry and from the Rikshospitalet hospital records. Information about traditional risk factors, immunosuppressive treatment, complications and hospitalisations were also retrieved. Comorbidity at transplantation (paper II) was quantified retrospectively using the Charlson Comorbidity Index, as described by Jassal et al (52). The calculation was individually performed for each patient based on review of hospital records.

3.1.2 Paper III

Medical files including survival data of all deceased donors older than 75 years, from whom single kidneys had been transplanted into recipients aged over 50 years, between 1990 and 2007, were retrieved and analysed. Data were retrieved from the same sources as for paper I and paper II. In addition, all graft biopsies obtained at transplantation and during the first

month post-transplantation were retrospectively analysed and scored by a blinded pathologist using both the Banff criteria (81) and the criteria defined by Remuzzi et al. (82).

3.1.3 Paper IV

Survival data for all patients starting dialysis in Norway between 1990 and 2005 were retrieved from the Norwegian Renal Registry. Patients accepted for transplantation and put on the transplantation waiting list were included in the study. Survival analyses using a time-dependant Cox model were performed in order to compare survival rates between transplanted patients and those remaining on the waiting list. In addition, clinical characteristics were retrieved from the registry and hospital records as described for the previous papers.

3.2 Statistics

A two-sided unpaired t-test or Mann-Whitney test was used, as appropriate, to compare groups. In paper I and II, the elderly recipient group was chosen as index for comparative analysis. Owing to the use of two tests to compare the index group versus the two other groups, Bonferroni correction was used and the level of significance for each test was set at 0.025 to achieve an overall level of significance of 0.05. Fisher's exact test was used to analyse binary data. We performed logistic regression analyses to identify risk factors for acute cellular rejection.

3.2.1 Survival analysis

Survival data were assessed using the Kaplan-Meier method, uni-/multivariate Cox regression analysis, and a time-dependent Cox model (paper IV). The Kaplan-Meier curves were compared by the log rank test. The events defined as end points in the analyses were patient death (all papers), death-censored graft loss (papers I-III) and uncensored graft loss (papers I-III). Patient survival was defined as time from transplantation (all papers) or from waiting list/start of dialysis (waitlist group, paper IV) to patient death or censoring due to loss from follow up (emigration), end of study or transplantation (waitlist group, paper IV). Graft survival was defined as the time from transplantation to patient death, time to loss of graft function with need of dialysis, or to censoring as described for patient death. The graft survival was analyzed in two different models, with or without censoring for death with functioning graft. The analyses were implemented using SPSS® 15.0.

3.2.2 Kaplan-Meier method

The Kaplan-Meier method is commonly used for estimation of survival probability (83;84). Survival is the time to a predefined event, for example death or graft loss used in the present studies. In addition to defining the event, it is also important to define a distinct starting point for survival. In randomised clinical trials (RCT), the survival time is usually measured from the time of randomisation. We chose the time of transplantation as baseline for survival analysis in papers I, II and III. In paper IV, the time of waitlisting or start of dialysis (latest for both) was used as the starting point for the waitlist group, whereas in the transplant group, it was set at the time of transplantation as in the previous papers.

A patient may be censored from the survival analysis if they are, for any reason except for the defined events, lost to follow up or no longer fulfil the inclusion criteria. The most typical example is a patient who has not experienced the event when the study is terminated. These patients will be censored owing to the end of study. In the case of graft survival, death with a functioning graft may be regarded as an event. On the other hand, however, it is not known how long the graft would have survived if the patient had not died. In this case, death with a functioning graft could also be censored, and not counted as an event. Patients who withdraw from the study, for example due to emigration or if a patient chooses to do so, can also be censored from the survival analysis.

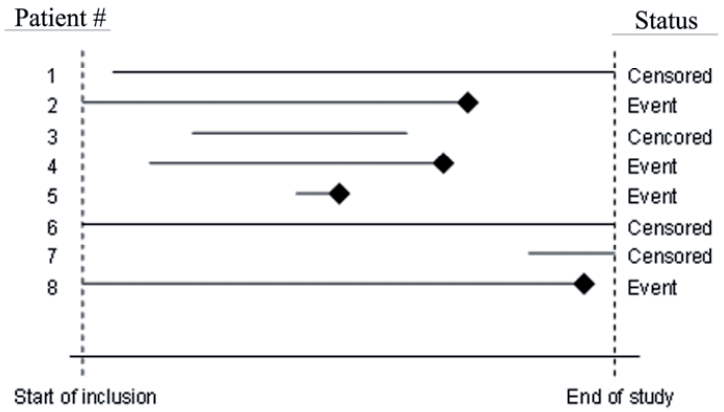

Figure 3. Survival of eight patients counted from date of inclusion in the study to reaching an event (♦) or to censoring due to loss of follow up (patient 3) or end of study (patient 1, 6 and 7). The length of each patient's line represents their event-free survival in the study.

By using the Kaplan-Meier method, survival in the future can be estimated by analysing data from the past. The probability of survival is calculated for each point of time an event has taken place. For example, if the first event takes place at day 7, the probability of not

having an event during the first 6 days is 1.0. The cumulative probability of survival can be expressed: $1{,}0 \cdot \left(\frac{n-y}{n} \right)$, where n is the total number at risk and y is the number of events.

If there are 10 patients at the start of the study (day 0), the probability of surviving day 7 is: $1.0 \cdot \left(\frac{10-1}{10} \right) = \underline{0.9}$. If the next event takes place at day 17, the probability of surviving the time period from day 7 throughout day 17 is: $\left(\frac{9-1}{9} \right) = \underline{0.89}$ and the cumulative survival probability from the start of study throughout day 17 is: $1.0 \cdot 0.9 \cdot 0.89 = \underline{0.8}$. If a patient is censored from the study between day 17 and day 33 when the next event takes place, this has to be taken into account when calculating the probability of survival during this interval. We know that 8 patients started this interval, one of them was censored, so only 7 survived until day 33 (n=7). In addition, one patient had an event at day 33 (y = 1) so 6 patients are left after day 33. The probability of survival from day 17 throughout day 33 is: $\left(\frac{7-1}{7} \right) = \underline{0.86}$ and the cumulative probability of surviving day 33 is: $0.8 \cdot 0.86 = \underline{0.69}$. By using these values for cumulative survival, we can construct a Kaplan-Meier plot illustrating how the survival decreases with time.

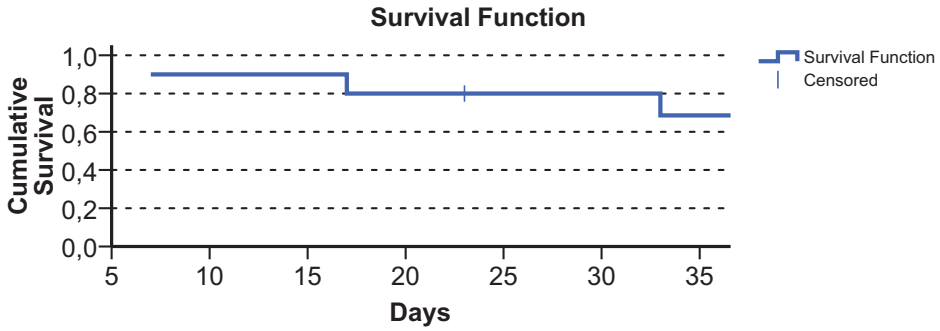

Figure 4. Cumulative survival illustrated with a Kaplan-Meier plot.

From the plot we can easily interpret the cumulative survival at different times. It is possible to compare the survival between two test groups by using the log rank test (85). The log rank test is principally a chi square test that compares the relationship between observed and expected values. H_0 for the test is that there is no difference between the survival curves of the two groups. The test is convenient to use when the curves do not cross each other and when there are more than 10 subjects in each group. It is important to know that the log rank test is purely a test of significance. It cannot provide either an estimate of the size of the difference between the groups or a confidence interval. The log rank test is further described in statistical textbooks (86;87).

3.2.3 Cox proportional hazard models

A Cox proportional hazard model determines the relationship between hazard rates in different groups of the patient population. It is possible to compare the survival of different patient groups and account for confounding effects (88). In a comparison of two different treatment protocols, the hazard rate for the standard treatment is $h_0(t)$ and $h_1(t)$ for the new treatment. If it is assumed that the relationship between the two hazard rates is constant at any point of time during the whole treatment period, the hazard rates are proportional:

$$\frac{h_1(t)}{h_0(t)} = \alpha \Rightarrow \; h_1(t) = h_0(t) \cdot \alpha \, .$$

The complexity and usefulness of the model can be increased by introducing and adjusting for more variables. To avoid negative values of α, it is convenient to define α as exp(β). With several variables included in the model, the equation for β is: $\beta = \beta_1 x_1 + \cdots\cdots + \beta_n x_n$, where $x_1, x_2, \cdots, x_n$ are values of a set of variables and $\beta_1, \beta_2, \cdots, \beta_3$ are regression coefficients. The variables can be continuous e.g. age, time on dialysis, cold ischaemic time,

or discrete e.g. gender or treatment modality etc. The general proportional hazard model can be expressed as $h(t) = h_0(t)exp(\beta_1 x_1 + \cdots\cdots + \beta_n x_n)$ where $h_0(t)$ is denoted as the 'baseline hazard'. The baseline hazard is a value that describes the hazard before new variables are included in the model. With this model, it is important that the variables are constant during the entire trial. If not, a model with a time dependant variable has to be used.

3.2.4 Time-dependant Cox model

In certain settings, as for example when the survival curves of the Kaplan-Meier plot cross each other as a result of changing hazards by time, it is necessary to create a model with a time dependant variable, to evaluate whether survival rates in the groups we are comparing are different from each other. In this case there is a time-varying risk factor (89). In paper IV, we defined two risk factors: 1) being on the waiting list and 2) transplantation. As many patients fall within both the waitlist and the transplant groups, they have two different hazards that need to be compared. In our model, we defined waitlist and transplantation as the two values of the time dependant variables. In addition we introduced several other possible confounders into the model as described in the result section, to ensure that the final result was also adjusted for these variables.

4. RESULTS

4.1 Paper I

In this paper, patient and graft outcomes in 301 ‘elderly’ kidney transplant recipients (≥ 70 years of age) were compared with 513 ‘senior’ recipients (60 – 69 years of age) and a ‘control’ group comprising 512 ‘average’ adult kidney recipients (age 45-54 years). A living donor transplantation was performed in 35% of patients; 17% in elderly recipients, 34% in senior recipients ($P < 0.001$) and 47% in control recipients ($P < 0.001$). Preemptive transplantation was performed in 19% of patients; 10% in elderly recipients, 18% in senior recipients ($P = 0.003$) and 25% in control recipients ($P < 0.001$). The elderly group had significantly lower rate of acute rejections during the first 12 weeks, compared with both the senior group ($P = 0.005$) and the control group ($P = 0.002$). Elderly and senior recipients had a higher incidence of death with a functioning graft during the follow-up: elderly 45%, senior 31% ($P < 0.001$), control 13% ($P < 0.001$). Five year patient survival was 56% in the elderly group, 72% in the senior group ($P < 0.001$) and 91% in the control group ($P < 0.001$). Cardiovascular disease (34%) and infection (27 %) were the most frequent causes of death. Five year graft survival was 53%, 70% and 84% in the elderly, senior and control groups, respectively. There were however no difference in graft survival when censoring for death with functioning graft. Consequently, the inferior graft survival in the elderly, reflects a natural higher risk of death with functioning graft.

4.2 Paper II

In this paper, potentially relevant clinical parameters for patient survival, graft survival and acute rejection were evaluated in 'elderly' (n = 354), 'senior' (n = 577) and 'control' (n = 563) recipients. Acute rejection during the first 90 days (HR 1.74 [1.34-2.25], P < 0.001), time on dialysis before transplantation (HR 1.02 per month [1.01-1.03], P < 0.001), and donor age ≥ 60 years (HR 1.52 [1.14-2.01], P = 0.004) were all associated with increased mortality in the elderly. Although comorbidity determined by the CCI score was not associated with increased mortality in the elderly group (HR 1.05 [0.98-1.12]), an association was found both in the senior (HR 1.17 per unit increase of the CCI score [1.08-1.27], P < 0.001), and control groups (HR 1.33 [1.19-1.48], P < 0.001). Delayed graft function (HR 3.69 [2.01-6.79], P < 0.001), donor age ≥ 60 years (HR 2.42 [1.30-4.49], P = 0.005) and presence of human leukocyte antigen (HLA) antibodies (HR 3.96 [1.38-11.37], P = 0.011) were independently associated with death-censored graft loss in the elderly. Treatment with AZA rather than MMF, any HLA-A or HLA-DR mismatch, donor age ≥ 60 years, and presence of HLA antibodies were associated with increased risk for early acute rejections (the first 90 days post- transplant) in all age groups.

4.3 Paper III

In this paper we investigated whether using kidneys from deceased donors with advanced age (older than 75 years) may be a way to increase the donor pool available for elderly patients with ESRD. Data from 54 single kidney transplantations using organs from 29 donors older than 75 (median 77.5, range 75.2-86.1) were assessed. Mean recipient age was 70.1 (range 50.6-82.4). 52 grafts (96%) had post-transplant function. Death-censored graft survival rates at 1, 3 and 5 years were 87%, 83% and 83%, respectively. Patient survival was 81%, 75% and 59% at the same time points. At follow up after a mean of 23 months (range 6-144 months), 35 recipients were alive with median serum creatinine level 163 µmol/L (range 103-348). Histological scores of graft biopsies obtained at transplantation and during the first month after transplantation did not predict graft outcome.

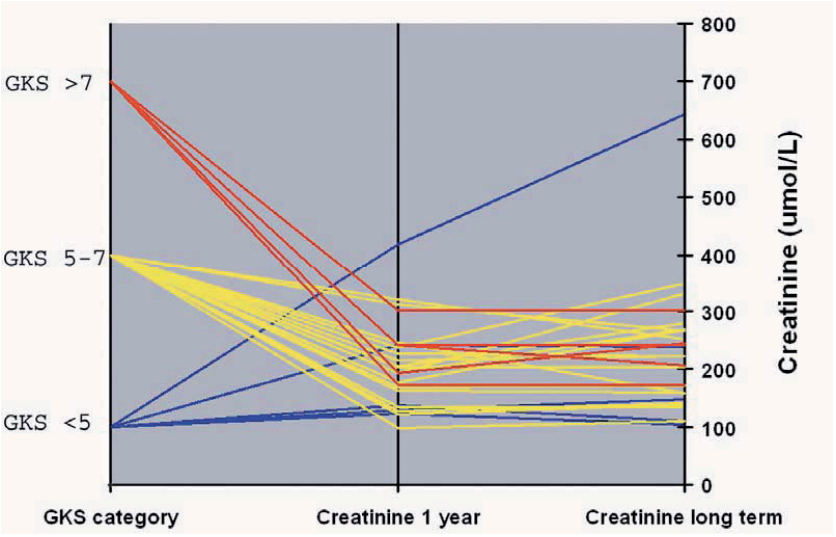

Figure 5. Graft outcome measured by serum creatinine after 1 year and at long term. Patients were categorized according to Global Kidney Score (GKS Banff) in graft biopsies obtained at transplantation.

4.4 Paper IV

In this paper we compared the survival of elderly kidney transplant recipients with similar aged patients who were accepted for transplantation but remained on dialysis. All patients older than 70 years who started dialysis between 1990 and 2005 and were waitlisted for kidney transplantation were included in the study. The patients were categorised according to the year dialysis was started (1990-1999 versus 2000-2005). Survival rates of 286 dialysis patients were analysed using a Kaplan-Meier model and a time-dependent Cox model. Comparisons were made between patients receiving a transplant and those who did not. In addition, the two time periods were compared. In the models, patients were censored from the waitlist group at the time of transplantation. The results were adjusted for age, sex, primary kidney disease, type of centre where dialysis was initiated (university vs. non university hospital), time on dialysis before waitlisting and dialysis modality. Patients starting dialysis between 1990 and 1999 had no significant long-term benefit of transplantation (HR for death 1.01 [0.58 – 1.75]). In contrast there was a substantial long-term benefit of transplantation among patients starting dialysis after 2000 (HR for death 0.40 [0.19 – 0.83], P = 0.014). Although transplant recipients had an increased risk of death during the first year after transplantation, they had a long-term cumulative survival benefit compared to those remaining on dialysis. The median survival after transplantation increased from 3.7 (3.0 – 4.4) years in the 1990 – 1999 cohort, to > 6.7 years in 2000 – 2007 cohort. For those who did not receive a kidney transplant, the median survival after time of waitlisting did not change between the two periods; 3.4 (3.3 – 3.7) years versus 3.1 (1.8 – 4.4) years.

5. DISCUSSION

5.1 Importance of results

5.1.1 Paper I

This paper describes the outcomes of elderly kidney transplant recipients at our centre, compared with slightly younger recipients. The survival rates are compared with those described previously in the literature. As expected, the survival of elderly recipients is inferior to that of younger ones. The inferior graft survival reflects a natural higher risk of death with a functioning graft in the elderly. We concluded that the five year patient survival of elderly recipients is acceptable and seems to be better than the survival of age-matched patients on dialysis for whom it is previously described five year patient survival up to 30-35 % (24;90). However, we did not directly compare the survival between transplant recipients and waitlisted patients remaining on dialysis. Since transplant recipients constitute a selected group of patients with less comorbidity than the average age-matched dialysis population, it is not possible to use the results of this study to draw the conclusion that, in elderly patients with ESRD, the prognosis is better after transplantation compared to continuing on dialysis. To investigate this issue further it was necessary to perform a study directly comparing two groups with relatively similar degree of comorbidity. The study was therefore important for launching the subsequent studies, especially the study presented in paper IV.

5.1.2 Paper II

The aim of the second paper was to define modifiable clinical parameters relevant to survival after kidney transplantation in elderly recipients. The presence of an acute rejection episode was identified as a variable strongly associated with poor survival. This indicates that it is very important, especially in elderly recipients, to establish an immunosuppressive protocol that prevents rejections. Interestingly, in the senior and control groups acute rejection was only associated with an increased risk of graft loss, not patient death. A possible explanation might be that whereas younger recipients lose their grafts in rejection, the elderly lose their lives because of complications to the rejection treatment. We also defined variables associated with the development of acute rejection episodes and these did not differ between the age groups. In addition, in the elderly group, time on dialysis and advanced donor age were also found to be modifiable variables significantly associated with patient survival. Somewhat surprising, the CCI score did not provide any prognostic information for the elderly, in contrast to the effect of the CCI score observed in the two younger age groups. Our interpretation is that the present screening algorithm used at our centre for selecting patients for transplantation worked sufficiently and in addition, in elderly recipients, age by itself is more important than presence of comorbid conditions. The fact that the median CCI score was only 3 in the elderly group supports the view that patients with serious comorbidity had been effectively disqualified from transplantation. Analyses of comorbidity in European patients requiring RRT indicate that even though comorbidity is an important predictor for mortality, the influence of comorbidity may be less important than expected when adjusted for confounders such as age, gender, primary renal disease, treatment modality and country (91). Reducing time on dialysis before transplantation to a minimum and avoidance of acute rejections should, therefore, be important aims of the treatment in the elderly ESRD population. An old-for-old allocation

strategy may be an effective way to reduce waiting time for aged recipients (76;92-95). However, the risk of using donors of advanced age for transplantation must be weighed against the alternative i.e. permanent dialysis. With increasing waiting lists and a lack of organs, this may be a risk worth taking in order to provide kidney transplants to elderly patients.

5.1.3 Paper III

Even if kidney transplantation is established as the treatment of choice for a relatively large number of selected elderly patients with ESRD, it may not be feasible owing to organ shortages and priority given to younger recipients. With long waiting times, many elderly patients will die or become unsuitable for transplantation before they are offered a transplant (96). Given the present situation with a scarcity of organs worldwide, it is necessary to increase the organ pool if transplantation is to be implemented as a realistic alternative for elderly patients. We suggest that a way of increasing the donor pool is to use organs from elderly deceased donors, that otherwise would not have been made available, to elderly recipients. It has been suggested that pre transplant histology score of the donor kidney might help predict outcome and long term graft function in organs from ECD (97). These "scoring systems" have not been sufficiently evaluated. Thus it is possible that current practice with selection of donor kidneys for transplantation based on donor age and pre-transplant histopathology leads to a reduced number of available kidneys for transplantation. We concluded that donor age and histopathology alone could not supply us with enough information to determine if a kidney should be used for transplantation or not. However, it is important to realize the limitations of the analyses. The study is based on results from a

single centre, it is retrospective and the numbers of ECD transplants are low. Therefore, the results should be interpreted with caution.

5.1.4 Paper IV

In the fourth paper, we directly compared the outcome of kidney transplantation with the outcome of continuing dialysis in patients older than 70 years accepted for transplantation. The most important findings were 1) transplant patient survival over the last decade is superior to dialysis patient survival, and 2) the outcome of transplantation has improved markedly with the intensification of immunosuppressive protocols. There was actually no survival benefit of transplantation in patients included before year 2000. We believe that the most important reason for the improvement of outcome is the change of immunosuppressive protocol that was performed in 2000, as there apart from differences in immunosuppression, virtually were no major baseline differences between the patients of the two time eras. As shown in previous studies (12;38), although transplant recipients have an increased risk of death during the first year after transplantation, there is a significant survival benefit beginning after 2.5 years. In other words, in a selected population of elderly patients with ESRD, kidney transplantation may be the treatment of choice. This supports the statement made by Knoll in a recent review: “Until further evidence emerges, nephrologists should continue to view all of their older patients with ESRD as potential transplant candidates. If functional status is reasonable and no obvious contraindication is present (e.g., recent malignancy), then transplant evaluation should proceed with screening for cardiovascular disease and malignancy as suggested by guidelines” (98).

5.2 Study Design

A prospective randomized clinical trial is generally regarded as the optimal scientific approach for evidence based medicine (99). However, performing RCTs to compare the outcomes of dialysis and transplantation would not be considered ethical owing to the superior quality of life associated with transplantation compared with dialysis. As a consequence, the present studies were given a retrospective, observational design. Using this approach, it is possible to generate and test a hypothesis by identifying significant associations between several factors and outcomes. The potential of an observational study to make causal inferences is however less compared to an RCT (100;101). With a retrospective design, it is important that the groups compared are as equal as possible. In the evaluation of the survival benefit of transplantation versus dialysis (paper IV), the differences in baseline characteristics between the waitlist and the transplant groups were small. Therefore we regard the results as representative and reliable, despite the limitations of the retrospective study design. Obviously, when comparing the outcome in different patient groups, it is also important that the groups are comparable with respect to important outcome parameters. For example, in paper I, it is not surprising that survival in patients aged 60 – 69 years is better than in patients aged greater than 70, knowing that age is one of the most important risk factors for death.

When comparing patients receiving a kidney transplant with those continuing on dialysis, it is extremely important to be aware of the basis used for selecting patients for transplantation. Just comparing the survival of kidney transplant recipients with patients on dialysis would be incorrect, since the patients with least comorbidity are selected for transplantation. In order to make the groups comparable, it was necessary to choose a criterion describing the patients' eligibility, namely being accepted for the transplant

waitlist. In paper II, it was important that all patients in the analysis were rigorously screened and treated for comorbidities before they were accepted for transplantation. In other words, our finding does not imply that comorbidity is not associated with the outcomes of kidney transplantation in elderly recipients. It only informs us that, in this age group, with the current established medical criteria for waitlisting, evaluation of comorbidity at transplantation does not help us predict patient outcome.

The precision of a study can be threatened by random errors. Random errors leads to increased variation of the data, but do not necessary interfere with the validity. On the other hand, systematic errors may bias the data in a way that threatens the validity of the study. Consequently, systematic errors are far more serious than random errors.

5.2.1 Internal validity

In the retrospective setting it is essential that the data collected are robust and reliable. If not, conclusions are drawn from unreliable sources ('garbage in – garbage out'). The internal validity of a study is the representativeness of results for the particular population being studied. A study can be biased due to selection of patients to the study (selection bias), due to the measurement of the variables (information bias) or because of missing or incomplete control for confounders.

Selection bias

Selection bias are distortions that result from the procedures used to select subjects and from factors that influence participation (87). By having only one transplant centre serving the whole country and well established routines for reporting data to the registry, the input of data has been very satisfactory. In addition, the data collected in the Norwegian Renal

Registry have been rigorously controlled by the leader of the registry since its establishment, and virtually all patients starting RRT in Norway are included. As a consequence, the data of the Norwegian Renal Registry are probably among the most robust renal registry data world-wide, and the risk of selection bias in the registry data should therefore be almost negligible. However, it is also important that the extraction of data is performed correctly. By a mistake, 53 'elderly', 64 'senior' and 51 'control' recipients transplanted between 1990 and 2005 were missed in the data extraction performed for paper I. The mistake was detected when an updated data set extraction for paper II was performed. However, a new survival analysis on the overall material revealed essentially the same results as originally published.

Information bias

Bias in evaluating an effect can occur from errors in obtaining the information. In addition to registry data, we also used data from hospital records to describe comorbidities, details of immunosuppressive treatment, and complications. Obviously, these data are more prone to individual variation, both by the surgeon/nephrologist responsible for registering data for the individual patient, and by the researcher extracting the data from the records. The variation caused by clinical data registration would mainly cause random errors influencing the precision of the estimates and not the validity. In order to make data extraction as consistent as possible, the process was performed by only one person. It is possible that this procedure may introduce a systematic information bias, for example because of misclassification of conditions giving score in the CCI. However, the finding that CCI score showed prognostic impact on the younger age groups, as expected from former analysis, supports the validity of our calculated indexes. The results could possibly have been even more robust if two researchers had performed the data extraction individually, compared results, and then reached consensus. The review of almost 1500 hospital records would

however be very time consuming, and we therefore decided to restrict this review procedure to one person.

Confounding

Confounding occurs when an investigator tries to determine the effect of an exposure on the outcome, but actually measures the effect of another factor, a confounding variable. A potential confounding variable has the following properties (102):

1. The variable must have an association with the disease i.e. it should be a risk factor for the disease
2. It must be associated with the exposure, which means that it must be unequally distributed between the exposed and the non-exposed groups
3. It must not be an effect of the exposure, nor be a factor in the causal pathway of the disease

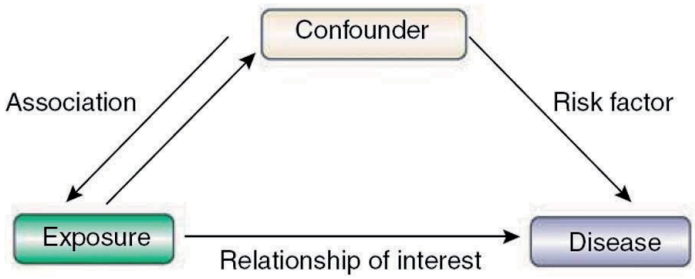

Figure 6. Properties of a confounder (102).
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There are different ways to address confounding during study design including randomisation, restriction or matching. Confounding may also be controlled by adjustments after completion of the study by using stratification or multivariate analysis. In paper IV, the

groups being compared are restricted as they have acceptance for transplantation as a criterion for inclusion. In addition, the background characteristics reveal only minor differences between those patients who were transplanted and those who were not. This may indicate that confounding was no major problem in the analysis. When adjusting for potential confounders it is essential to know the value of the suspected variable. For instance, smoking is known to be a risk factor for cardiac death and is therefore a potential confounder in the survival analyses. Unfortunately, reliable information about smoking was not available in our data set and by this; we were not available to control our analyses for smoking habits.

5.2.2 External validity

External validity or generalization describes the relevance of the study to a specified patient population. Although RRT is conducted at several nephrology units throughout the country, the transplant activity is centralized at Rikshospitalet. The study, therefore, uses data from a single transplant centre, which may be regarded as a limitation. It could be claimed that the study describes the results of a national transplant policy that is not applicable to other countries. However, the fact that all patients have been treated at the same transplant centre, following the same acceptance criteria, and the same standard immunosuppressive protocol, makes these data robust and may also bring additional strength to the study. Furthermore, the robust and complete national Norwegian registry of RRT patients has made it possible to perform the study with almost no patients being lost to follow up.

5.3 Methods

5.3.1 Kaplan-Meier method

The Kaplan-Meier method has already been described in detail. Even though the results are estimates of survival and not actual survival figures, the Kaplan-Meier method is generally accepted as the best way to describe survival. If a high percentage of patients included in the analysis reach an event, as was the case in our studies, the result becomes more representative of actual survival. Comparing survival between groups of patients by the log rank test is also well established in the literature (83-85). However, when the survival curves cross each other due to a change of risk in one of the groups, the log rank test is no longer applicable. In this situation it is necessary to introduce a time dependant variable as we did in paper IV.

5.3.2 Cox regression

The Cox proportional hazard regression method is widely accepted as a tool for identifying variables which impact on the outcome in survival studies. It is important to select the variables tested in the model based on best clinical knowledge. By introducing several variables and combining them in a multivariate model, it is possible to adjust the variables for each other and thereby get closer to the real independent impact of each factor. The number of variables included in the model should, as a rule, not exceed 10 % or the square root of the number of events (86). If there are a large number of potential explanatory variables, the variables eventually included in the multivariate model may first be tested in a univariate analysis. Only those variables having significant or near significant influence in the univariate analysis should then be implemented into the multivariate model. In our

analysis of variables associated with patient death in paper II, there were 237 events in the elderly group, and after univariate testing, we eventually implemented 13 variables into the multivariate model. When selecting variables, it is also important to be aware of the effect of, and adjust for, confounding factors. In addition, during the interpretation of the results, it is important to be aware that there may exist unknown or unmeasured confounders not implemented in the model.

5.4 Ethical considerations

In the context of organ shortage, transplantation of elderly patients may become an ethical issue. Even if we have justified that kidney transplantation, when successful, improves both the survival and the quality of life for selected elderly patients with ESRD, an ethical dilemma arises when a kidney is allocated to an elderly person implicating that a young person on the waiting list has to wait longer for an appropriate organ. On the other hand, elderly patients are more likely to die on the waiting list, and it is therefore important to reduce the waiting time as much as possible. It is possible to increase the organ pool by increased use of ECDs as we have described in paper III. An old-for-old policy like this could make it possible to allocate ECD kidneys to elderly recipients on the deceased donor waiting list, and thereby reduce their time on dialysis. This can be implemented without simultaneously increasing the waiting time for younger patients on the list. Giving organs of potential "lower-quality" to elderly recipients, raises further both moral and ethical considerations. The policy of using ECD to older recipients has, however, already been adopted with success in several countries, and elderly transplant candidates are among those who are most likely to receive optimal benefit from ECD kidneys (103).

6. CONCLUSIONS AND IMPLICATIONS

6.1 Paper I

We found no difference in graft survival between elderly, senior and control patients when censored for death with a functioning graft. As expected, the elderly and senior recipients had inferior survival, compared with the control group. Given the poor prognosis of these patients in dialysis we consider a 5-year patient survival rate of 56% in patients over 70 years of age to be acceptable. Elderly patients with ESRD should be considered for transplantation, and a selected group should be offered the option.

6.2 Paper II

Long time on dialysis was associated with reduced survival in kidney transplant recipients over 70 years of age. Low acute rejection rates improved outcomes for elderly kidney recipients. CCI score at transplantation did not provide a benefit in the selection of elderly patients for kidney transplantation, although it is known to be useful in younger patients. To obtain the best results, treatment of elderly recipients should aim at reducing time on dialysis before transplantation and avoid acute rejection episodes.

6.3 Paper III

Kidneys from deceased donors over 75 years perform acceptably as single transplants and should be considered for use in elderly recipients. Two selected histological graft score systems gave no supplementary information on the long-term outcome of the graft.

6.4 Paper IV

Elderly patients (≥ 70 years old) on dialysis treatment, who fulfil the established medical criteria for transplantation, have improved survival following kidney transplantation, compared with patients accepted for transplantation but continuing dialysis. There has been a substantial improvement in long-term survival over the last decade, partly due to a more potent immunosuppressive protocol. Given a sufficient supply of organs, transplantation may be the preferred treatment for selected elderly patients with ESRD.

6.5 Answers to the research questions

Our initial key questions may be answered as follows:

1. **Kidney transplantation is safe for selected elderly ESRD patients and should be the preferred treatment without an upper age limit.**
2. **Time on dialysis prior to transplantation and frequency of acute rejection episodes are modifiable clinical variables relevant to improve kidney transplantation outcomes in the elderly.**
3. **Kidneys from old deceased donors should not be discarded just because of advanced age.**
4. **Kidney transplantation is superior to dialysis in elderly patients with ESRD fulfilling the established criteria for acceptance onto a kidney transplant waiting list.**

7. FUTURE RESEARCH

7.1 Health economic analyses

Our project was not designed as a health economic study. We have, therefore, not evaluated the economic aspects of transplantation versus continuing dialysis in our elderly study population. Previous studies have revealed that kidney transplantation is the most cost-effective and preferred mode of RRT (33;104). In a paper from Sweden, the annual cost of RRT is estimated to be $70,796 for a patient on haemodialysis, and $46,018 for a patient on peritoneal dialysis. Kidney transplantation is estimated to cost $70,000 during the first year, and $14,159 per year thereafter with a functioning transplant (105). Obviously, the exact costs will vary between countries depending on the organisation and financing of medical care in each country. The costs may also vary according to the age of the patients. A health economic study comparing the costs related to various types of RRT will, therefore, provide important information to help determine future priorities for RRT.

7.2 Prospective evaluation of comorbidity

It may not be possible to perform an RCT comparing the outcomes of kidney transplantation with dialysis. However, it may be possible to investigate the impact of comorbidity in a prospective manner. If comorbidity data (CCI) was reported systematically to the registry at the start of RRT and at the time of transplantation, the effect of comorbidity could be studied prospectively, not only in the elderly, but in all age groups.

7.3 Immunosuppression

In paper II we found an association between acute rejection episodes and poor survival in elderly kidney transplant recipients. In paper IV we found that there were significant improvements in survival after the introduction of newer and more potent immunosuppressive protocols. In the retrospective setting, however, we cannot provide evidence for the causal inference between the level of immunosuppression and the outcome. It has been proposed that MMF is perhaps less safe than AZA in the elderly (106), but our study has shown that survival has improved over the last decade following the introduction of MMF. Furthermore it is debated whether other strategies as for example induction therapy with thymoglobulin/IL-2R antagonist agents or delayed introduction/avoidance of calcineurin inhibitors, may be beneficial in a setting with elderly donors and recipients (107-110). There is definitely a need for further prospective studies evaluating optimal immunosuppression strategies in elderly recipients (111).

7.4. Graft preservation

It is possible, and likely, that grafts from ECDs may benefit from improved methods of graft preservation including artificial extra-corporeal circulation of the graft (112) and new perfusion solutions. In addition, the ideal balance between short ischaemia time and good immunological match has yet to be established.

8. REFERENCES

(1) Hamilton DN, Reid WA. Yu. Yu. Voronoy and the first human kidney allograft. Surg Gynecol Obstet 1984 Sep;159(3):289-94.

(2) Matevossian E, Kern H, Huser N, Doll D, Snopok Y, Nahrig J, et al. Surgeon Yurii Voronoy (1895-1961) - a pioneer in the history of clinical transplantation: in memoriam at the 75th anniversary of the first human kidney transplantation. Transpl Int 2009 Dec;22(12):1132-9.

(3) Barry JM, Murray JE. The first human renal transplants. J Urol 2006 Sep;176(3):888-90.

(4) Merrill JP, Murray JE, Harrison JH, Guild WR. Successful homotransplantation of the human kidney between identical twins. J Am Med Assoc 1956 Jan 28;160(4):277-82.

(5) Dealy JB, Jr., Dammin GJ, Murray JE, Merrill JP. Total body irradiation in man: tissue patterns observed in attempts to increase the receptivity of renal homografts. Ann N Y Acad Sci 1960 May 31;87:572-85.

(6) Kuss R, Legrain M, Mathe G, Nedey R, Camey M. Homologous human kidney transplantation. Experience with six patients. Postgrad Med J 1962 Sep;38:528-31.

(7) Merrill JP, Murray JE, Takacs FJ, Hager EB, Wilson RE, Dammin GJ. Successful transplantation of kidney from a human cadaver. JAMA 1963 Aug 3;185:347-53.

(8) Murray JE, Merrill JP, Harrison JH, Wilson RE, Dammin GJ. Prolonged survival of human-kidney homografts by immunosuppressive drug therapy. Ann Plast Surg 1984 Jan;12(1):70-83.

(9) Calne RY, Wood AJ. Cyclosporin in cadaveric renal transplantation: 3-year follow-up of a European multicentre trial. Lancet 1985 Sep 7;2(8454):549.

(10) Calne RY. Cyclosporin in cadaveric renal transplantation: 5-year follow-up of a multicentre trial. Lancet 1987 Aug 29;2(8557):506-7.

(11) Kainz A, Heinze G, Korbely R, Schwarz C, Oberbauer R. Mycophenolate mofetil use is associated with prolonged graft survival after kidney transplantation. Transplantation 2009 Nov 15;88(9):1095-100.

(12) Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med 1999 Dec 2;341(23):1725-30.

(13) Westlie L. Norsk nyremedisin. Et moderne eventyr. 1999.

(14) Statistisk Sentralbyrå. 2008 NovemberAvailable from: URL: www.ssb.no

(15) Sardon J-P. Recent Demographic Trends in the Developed Countries. 2006 [cited 2009 Oct 12];Available from: URL: http://www.ined.fr/en/pop_figures/developed_countries

(16) World Population Prospects: The 2008 Revision. 2009 March 11Available from: URL: http:esa.un.org/unpp

(17) Whaley-Connell AT, Sowers JR, Stevens LA, McFarlane SI, Shlipak MG, Norris KC, et al. CKD in the United States: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. Am J Kidney Dis 2008 Apr;51(4 Suppl 2):S13-S20.

(18) Collins AJ, Foley RN, Herzog C, Chavers B, Gilbertson D, Ishani A, et al. United States Renal Data System 2008 Annual Data Report Abstract. Am J Kidney Dis 2009 Jan;53(1 Suppl):vi-374.

(19) Leivestad T. Årsrapport fra Norsk Nefrologiregister for 2008. 2009 [cited 2009 Oct 28];Available from: URL: www.nephro.no/nnr.html

(20) Conway B, Webster A, Ramsay G, Morgan N, Neary J, Whitworth C, et al. Predicting mortality and uptake of renal replacement therapy in patients with stage 4 chronic kidney disease. Nephrol Dial Transplant 2009 Jun;24(6):1930-7.

(21) Danovitch GM, Cohen DJ, Weir MR, Stock PG, Bennett WM, Christensen LL, et al. Current status of kidney and pancreas transplantation in the United States, 1994-2003. Am J Transplant 2005 Apr;5(4 Pt 2):904-15.

(22) Jager KJ, van Dijk PC, Dekker FW, Stengel B, Simpson K, Briggs JD. The epidemic of aging in renal replacement therapy: an update on elderly patients and their outcomes. Clin Nephrol 2003 Nov;60(5):352-60.

(23) Kurella M, Covinsky KE, Collins AJ, Chertow GM. Octogenarians and nonagenarians starting dialysis in the United States. Ann Intern Med 2007 Feb 6;146(3):177-83.

(24) Macrae J, Friedman AL, Friedman EA, Eggers P. Live and deceased donor kidney transplantation in patients aged 75 years and older in the United States. Int Urol Nephrol 2005;37(3):641-8.

(25) Port FK, Merion RM, Roys EC, Wolfe RA. Trends in organ donation and transplantation in the United States, 1997-2006. Am J Transplant 2008 Apr;8(4 Pt 2):911-21.

(26) Kramer A, Stel V, Zoccali C, Heaf J, Ansell D, Gronhagen-Riska C, et al. An update on renal replacement therapy in Europe: ERA-EDTA Registry data from 1997 to 2006. Nephrol Dial Transplant 2009 Oct 9.

(27) Murtagh FE, Marsh JE, Donohoe P, Ekbal NJ, Sheerin NS, Harris FE. Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. Nephrol Dial Transplant 2007 Jul;22(7):1955-62.

(28) Tazza L, Di NA, Bossola M, Valle S, Pezzotti P, Luciani G, et al. Ageing of patients on chronic dialysis: effects on mortality--a 12-year study. Nephrol Dial Transplant 2009 Mar;24(3):940-7.

(29) Couchoud C, Labeeuw M, Moranne O, Allot V, Esnault V, Frimat L, et al. A clinical score to predict 6-month prognosis in elderly patients starting dialysis for end-stage renal disease. Nephrol Dial Transplant 2009 May;24(5):1553-61.

(30) Mauri JM, Cleries M, Vela E. Design and validation of a model to predict early mortality in haemodialysis patients. Nephrol Dial Transplant 2008 May;23(5):1690-6.

(31) Mendelssohn DC, Mujais SK, Soroka SD, Brouillette J, Takano T, Barre PE, et al. A prospective evaluation of renal replacement therapy modality eligibility. Nephrol Dial Transplant 2009 Feb;24(2):555-61.

(32) Kontodimopoulos N, Niakas D. An estimate of lifelong costs and QALYs in renal replacement therapy based on patients' life expectancy. Health Policy 2008 Apr;86(1):85-96.

(33) Niakas D, Kontodimopoulos N. Is renal transplantation the most cost-effective and preferable therapy for patients suffering from end-stage renal disease or not? Health Policy 2009 Mar;89(3):329-31.

(34) Rebollo P, Ortega F, Baltar JM, Badia X, Alvarez-Ude F, Diaz-Corte C, et al. Health related quality of life (HRQOL) of kidney transplanted patients: variables that influence it. Clin Transplant 2000 Jun;14(3):199-207.

(35) Vincenti F. A decade of progress in kidney transplantation. Transplantation 2004 May 15;77(9 Suppl):S52-S61.

(36) Oniscu GC, Brown H, Forsythe JL. How great is the survival advantage of transplantation over dialysis in elderly patients? Nephrol Dial Transplant 2004 Apr;19(4):945-51.

(37) Oniscu GC, Brown H, Forsythe JL. How old is old for transplantation? Am J Transplant 2004 Dec;4(12):2067-74.

(38) Rao PS, Merion RM, Ashby VB, Port FK, Wolfe RA, Kayler LK. Renal transplantation in elderly patients older than 70 years of age: results from the Scientific Registry of Transplant Recipients. Transplantation 2007 Apr 27;83(8):1069-74.

(39) Sener A, Schweitzer EJ, Munivenkatappa R, Cooper M, Bartlett ST, Philosophe B, et al. Deceased-donor renal transplantation in the geriatric population demonstrates equal graft survival compared with younger recipients. Transplantation 2009 May 27;87(10):1549-54.

(40) Organ Procurement and Transplantation Network. OPTN 2009 September 11Available from: URL: http://optn.transplant.hrsa.gov/latestData/rptData.asp

(41) de Fijter JW. An old virtue to improve senior programs. Transpl Int 2009 Mar;22(3):259-68.

(42) Bayat S, Kessler M, Briancon S, Frimat L. Survival of transplanted and dialysed patients in a French region with focus on outcomes in the elderly. Nephrol Dial Transplant 2009 Sep 11.

(43) Johnson DW, Herzig K, Purdie D, Brown AM, Rigby RJ, Nicol DL, et al. A comparison of the effects of dialysis and renal transplantation on the survival of older uremic patients. Transplantation 2000 Mar 15;69(5):794-9.

(44) Mendonca HM, Dos Reis MA, de Castro de Cintra Sesso, Camara NO, Pacheco-Silva A. Renal transplantation outcomes: a comparative analysis between elderly and younger recipients. Clin Transplant 2007 Nov;21(6):755-60.

(45) Saidi RF, Kennealey PT, Elias N, Kawai T, Hertl M, Farrell M, et al. Deceased donor kidney transplantation in elderly patients: is there a difference in outcomes? Transplant Proc 2008 Dec;40(10):3413-7.

(46) Shah T, Bunnapradist S, Hutchinson I, Pravica V, Cho YW, Mendez R, et al. The evolving notion of "senior" kidney transplant recipients. Clin Transplant 2008 Nov;22(6):794-802.

(47) Humar A, Denny R, Matas AJ, Najarian JS. Graft and quality of life outcomes in older recipients of a kidney transplant. Exp Clin Transplant 2003 Dec;1(2):69-72.

(48) Laupacis A, Keown P, Pus N, Krueger H, Ferguson B, Wong C, et al. A study of the quality of life and cost-utility of renal transplantation. Kidney Int 1996 Jul;50(1):235-42.

(49) Rebollo P, Ortega F, Baltar JM, Diaz-Corte C, Navascues RA, Naves M, et al. Health-related quality of life (HRQOL) in end stage renal disease (ESRD) patients over 65 years. Geriatr Nephrol Urol 1998;8(2):85-94.

(50) Petersen E, Baird BC, Shihab F, Koford JK, Chelamcharla M, Habib A, et al. The impact of recipient history of cardiovascular disease on kidney transplant outcome. ASAIO J 2007 Sep;53(5):601-8.

(51) Aalten J, Hoogeveen EK, Roodnat JI, Weimar W, Borm GF, de Fijter JW, et al. Associations between pre-kidney-transplant risk factors and post-transplant cardiovascular events and death. Transpl Int 2008 Oct;21(10):985-91.

(52) Jassal SV, Schaubel DE, Fenton SS. Baseline comorbidity in kidney transplant recipients: a comparison of comorbidity indices. Am J Kidney Dis 2005 Jul;46(1):136-42.

(53) Wu C, Shapiro R, Tan H, Basu A, Smetanka C, Morgan C, et al. Kidney transplantation in elderly people: the influence of recipient comorbidity and living kidney donors. J Am Geriatr Soc 2008 Feb;56(2):231-8.

(54) Courtney AE, Maxwell AP. The challenge of doing what is right in renal transplantation: balancing equity and utility. Nephron Clin Pract 2009;111(1):c62-c67.

(55) Euorotransplant Annual Report 2008. 2009 September 24Available from: URL: http://www.eurotransplant.nl/?id=annual_report

(56) Gill J, Bunnapradist S, Danovitch GM, Gjertson D, Gill JS, Cecka M. Outcomes of kidney transplantation from older living donors to older recipients. Am J Kidney Dis 2008 Sep;52(3):541-52.

(57) Gill JS, Gill J, Rose C, Zalunardo N, Landsberg D. The older living kidney donor: Part of the solution to the organ shortage. Transplantation 2006 Dec 27;82(12):1662-6.

(58) Hartmann A, Fauchald P, Westlie L, Brekke IB, Holdaas H. The risk of living kidney donation. Nephrol Dial Transplant 2003 May;18(5):871-3.

(59) Ibrahim HN, Foley R, Tan L, Rogers T, Bailey RF, Guo H, et al. Long-term consequences of kidney donation. N Engl J Med 2009 Jan 29;360(5):459-69.

(60) Oien CM, Reisaeter AV, Leivestad T, Dekker FW, Line PD, Os I. Living donor kidney transplantation: the effects of donor age and gender on short- and long-term outcomes. Transplantation 2007 Mar 15;83(5):600-6.

(61) Akoh JA, Denton MD, Bradshaw SB, Rana TA, Walker MB. Early results of a controlled non-heart-beating kidney donor programme. Nephrol Dial Transplant 2009 Jun;24(6):1992-6.

(62) Barlow AD, Metcalfe MS, Johari Y, Elwell R, Veitch PS, Nicholson ML. Case-matched comparison of long-term results of non-heart beating and heart-beating donor renal transplants. Br J Surg 2009 Jun;96(6):685-91.

(63) Locke JE, Segev DL, Warren DS, Dominici F, Simpkins CE, Montgomery RA. Outcomes of kidneys from donors after cardiac death: implications for allocation and preservation. Am J Transplant 2007 Jul;7(7):1797-807.

(64) Reich DJ, Mulligan DC, Abt PL, Pruett TL, Abecassis MM, D'Alessandro A, et al. ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation. Am J Transplant 2009 Sep;9(9):2004-11.

(65) Wells AC, Rushworth L, Thiru S, Sharples L, Watson CJ, Bradley JA, et al. Donor kidney disease and transplant outcome for kidneys donated after cardiac death. Br J Surg 2009 Mar;96(3):299-304.

(66) Tilney N, Murray J, Thistlethwaite R, Norman D, Delmonico F, Hanto D, et al. Promotion of altruistic donation. Transplantation 2009 Sep 27;88(6):847.

(67) Rosendale JD, Chabalewski FL, McBride MA, Garrity ER, Rosengard BR, Delmonico FL, et al. Increased transplanted organs from the use of a standardized donor management protocol. Am J Transplant 2002 Sep;2(8):761-8.

(68) Rigotti P, Ekser B, Furian L, Baldan N, Valente ML, Boschiero L, et al. Outcome of renal transplantation from very old donors. N Engl J Med 2009 Apr 2;360(14):1464-5.

(69) Schold JD, Howard RJ, Scicchitano MJ, Meier-Kriesche HU. The expanded criteria donor policy: an evaluation of program objectives and indirect ramifications. Am J Transplant 2006 Jul;6(7):1689-95.

(70) Zuckerman JM, Singh RP, Farney AC, Rogers J, Stratta RJ. Single center experience transplanting kidneys from deceased donors with terminal acute renal failure. Surgery 2009 Oct;146(4):686-94.

(71) Baskin-Bey ES, Nyberg SL. Matching graft to recipient by predicted survival: can this be an acceptable strategy to improve utilization of deceased donor kidneys? Transplant Rev (Orlando) 2008 Jul;22(3):167-70.

(72) Metzger RA, Delmonico FL, Feng S, Port FK, Wynn JJ, Merion RM. Expanded criteria donors for kidney transplantation. Am J Transplant 2003;3 Suppl 4:114-25.

(73) Port FK, Bragg-Gresham JL, Metzger RA, Dykstra DM, Gillespie BW, Young EW, et al. Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. Transplantation 2002 Nov 15;74(9):1281-6.

(74) Meier-Kriesche HU, Schold JD, Gaston RS, Wadstrom J, Kaplan B. Kidneys from deceased donors: maximizing the value of a scarce resource. Am J Transplant 2005 Jul;5(7):1725-30.

(75) Rao PS, Schaubel DE, Guidinger MK, Andreoni KA, Wolfe RA, Merion RM, et al. A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. Transplantation 2009 Jul 27;88(2):231-6.

(76) Frei U, Noeldeke J, Machold-Fabrizii V, Arbogast H, Margreiter R, Fricke L, et al. Prospective age-matching in elderly kidney transplant recipients--a 5-year analysis of the Eurotransplant Senior Program. Am J Transplant 2008 Jan;8(1):50-7.

(77) Wolfe RA, McCullough KP, Schaubel DE, Kalbfleisch JD, Murray S, Stegall MD, et al. Calculating life years from transplant (LYFT): methods for kidney and kidney-pancreas candidates. Am J Transplant 2008 Apr;8(4 Pt 2):997-1011.

(78) Hallan SI, Coresh J, Astor BC, Asberg A, Powe NR, Romundstad S, et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. J Am Soc Nephrol 2006 Aug;17(8):2275-84.

(79) Jakobsen A, Albrechtsen D, Leivestad T. Renal transplantation--the Norwegian model. Ann Transplant 1996;1(3):32-5.

(80) Fauchald P, Albrechtsen D, Leivestad T, Berg KJ, Talseth T, Flatmark A. Renal replacement therapy in elderly patients. Transpl Int 1988 Oct;1(3):131-4.

(81) Lopes JA, Moreso F, Riera L, Carrera M, Ibernon M, Fulladosa X, et al. Evaluation of pre-implantation kidney biopsies: comparison of Banff criteria to a morphometric approach. Kidney Int 2005 Apr;67(4):1595-600.

(82) Remuzzi G, Grinyo J, Ruggenenti P, Beatini M, Cole EH, Milford EL, et al. Early experience with dual kidney transplantation in adults using expanded donor criteria. Double Kidney Transplant Group (DKG). J Am Soc Nephrol 1999 Dec;10(12):2591-8.

(83) Bland JM, Altman DG. Survival probabilities (the Kaplan-Meier method). BMJ 1998 Dec 5;317(7172):1572.

(84) Jager KJ, van Dijk PC, Zoccali C, Dekker FW. The analysis of survival data: the Kaplan-Meier method. Kidney Int 2008 Sep;74(5):560-5.

(85) Bland JM, Altman DG. The logrank test. BMJ 2004 May 1;328(7447):1073.

(86) Altman DG. Practical Statistics for Medical Research. Chapman & Hall/CRC; 1991.

(87) Rothman K, Greenland S. Modern Epidemiology, Second edition. Lippincot Williams & Wilkins; 1998.

(88) van Dijk PC, Jager KJ, Zwinderman AH, Zoccali C, Dekker FW. The analysis of survival data in nephrology: basic concepts and methods of Cox regression. Kidney Int 2008 Sep;74(6):705-9.

(89) Dekker FW, de MR, van Dijk PC, Zoccali C, Jager KJ. Survival analysis: time-dependent effects and time-varying risk factors. Kidney Int 2008 Oct;74(8):994-7.

(90) ERA-EDTA Registry:ERA-EDTA Registry Annual Report 2007. Academic Medical Center,Department of Medical Informatics,Amsterdam,The Netherlands 2009.

(91) van Manen JG, van Dijk PCW, Stel VS, Dekker FW, Cleries M, Conte F, et al. Confounding effect of comorbidity in survival studies in patients on renal replacement therapy. Nephrology Dialysis Transplantation 2007 Jan 1;22(1):187-95.

(92) Fritsche L, Horstrup J, Budde K, Reinke P, Giessing M, Tullius S, et al. Old-for-old kidney allocation allows successful expansion of the donor and recipient pool. Am J Transplant 2003 Nov;3(11):1434-9.

(93) Giessing M, Budde K, Fritsche L, Slowinski T, Tuerk I, Schoenberger B, et al. "Old-for-old" cadaveric renal transplantation: surgical findings, perioperative complications and outcome. Eur Urol 2003 Dec;44(6):701-8.

(94) Giessing M, Fuller TF, Friedersdorff F, Deger S, Wille A, Neumayer HH, et al. Outcomes of transplanting deceased-donor kidneys between elderly donors and recipients. J Am Soc Nephrol 2009 Jan;20(1):37-40.

(95) Moers C, Kornmann NS, Leuvenink HG, Ploeg RJ. The influence of deceased donor age and old-for-old allocation on kidney transplant outcome. Transplantation 2009 Aug 27;88(4):542-52.

(96) Schold J, Srinivas TR, Sehgal AR, Meier-Kriesche HU. Half of kidney transplant candidates who are older than 60 years now placed on the waiting list will die before receiving a deceased-donor transplant. Clin J Am Soc Nephrol 2009 Jul;4(7):1239-45.

(97) Remuzzi G, Cravedi P, Perna A, Dimitrov BD, Turturro M, Locatelli G, et al. Long-term outcome of renal transplantation from older donors. N Engl J Med 2006 Jan 26;354(4):343-52.

(98) Knoll G. Is Kidney Transplantation for Everyone? The Example of the Older Dialysis Patient. Clin J Am Soc Nephrol 2009 Nov 12.

(99) Stel VS, Zoccali C, Dekker FW, Jager KJ. The Randomized Controlled Trial. Nephron Clin Pract 2009 Sep 11;113(4):c337-c342.

(100) Jager KJ, Stel VS, Wanner C, Zoccali C, Dekker FW. The valuable contribution of observational studies to nephrology. Kidney Int 2007 Sep;72(6):671-5.

(101) Stel VS, Jager KJ, Zoccali C, Wanner C, Dekker FW. The randomized clinical trial: an unbeatable standard in clinical research? Kidney Int 2007 Sep;72(5):539-42.

(102) Jager KJ, Zoccali C, Macleod A, Dekker FW. Confounding: what it is and how to deal with it. Kidney Int 2008 Feb;73(3):256-60.

(103) Gaston RS, Danovitch GM, Adams PL, Wynn JJ, Merion RM, Deierhoi MH, et al. The report of a national conference on the wait list for kidney transplantation. Am J Transplant 2003 Jul;3(7):775-85.

(104) Abecassis M, Bartlett ST, Collins AJ, Davis CL, Delmonico FL, Friedewald JJ, et al. Kidney transplantation as primary therapy for end-stage renal disease: a National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQITM) conference. Clin J Am Soc Nephrol 2008 Mar;3(2):471-80.

(105) Wikstrom B, Fored M, Eichleay MA, Jacobson SH. The financing and organization of medical care for patients with end-stage renal disease in Sweden. Int J Health Care Finance Econ 2007 Dec;7(4):269-81.

(106) Johnson DW, Nicol DL, Purdie DM, Preston JM, Brown AM, Hawley CM, et al. Is mycophenolate mofetil less safe than azathioprine in elderly renal transplant recipients? Transplantation 2002 Apr 15;73(7):1158-63.

(107) Andres A, Budde K, Clavien PA, Becker T, Kessler M, Pisarski P, et al. A randomized trial comparing renal function in older kidney transplant patients following delayed versus immediate tacrolimus administration. Transplantation 2009 Nov 15;88(9):1101-8.

(108) Arbogast H, Huckelheim H, Schneeberger H, Illner WD, Tarabichi A, Fertmann J, et al. A calcineurin antagonist-free induction/maintenance strategy for immunosuppression in elderly recipients of renal allografts from elderly cadaver donors: long-term results from a prospective single centre trial. Clin Transplant 2005 Jun;19(3):309-15.

(109) Gavela ME, Sancho CA, Escudero Q, V, Ávila Bernabeu AI, Beltran CS, Morales Garcia AI, et al. Induction treatment with low-dose thymoglobulin or basiliximab in renal transplants from older donors. Transplant Proc 2008 Nov;40(9):2900-2.

(110) Hardinger KL, Brennan DC, Schnitzler MA. Rabbit antithymocyte globulin is more beneficial in standard kidney than in extended donor recipients. Transplantation 2009 May 15;87(9):1372-6.

(111) Danovitch GM, Gill J, Bunnapradist S. Immunosuppression of the elderly kidney transplant recipient. Transplantation 2007 Aug 15;84(3):285-91.

(112) Moers C, Smits JM, Maathuis MH, Treckmann J, van GF, Napieralski BP, et al. Machine perfusion or cold storage in deceased-donor kidney transplantation. N Engl J Med 2009 Jan 1;360(1):7-19.

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