Aus der Medizinischen Klinik mit Schwerpunkt

Nephrologie und Intern. Intensivmedizin der Medizinischen Fakultät der

Charité – Universitätsmedizin Berlin

DISSERTATION

„Five Year Analysis of the Eurotransplant Senior Program"

Zur Erlangung des akademischen Grades

Doctor rerum medicarum (Dr. rer. medic.)

vorgelegt der Medizinischen Fakultät der Charité – Universitätsmedizin

Berlin

von

Jana Nöldeke

aus Berlin

Gutachter: 1. Prof. Dr. med. U. Frei, Berlin

2. Prof. Dr. med. G. Wolf, Jena

3. PD Dr. med. S. Tullius, Boston

Datum der Promotion: 25. November 2005

Abstrakt (deutsch)

Der stete Anstieg des Durchschnittalters unsere Gesellschaft und der Mangel an Spenderorganen stellen eine bedeutende Herausforderung für die Organtransplantation dar. In Folge des immer höher werdenden Alters der Nierentransplantatspender und – Empfänger ist die Nierentransplantation schon lange nicht mehr auf junge Patienten mit terminaler Niereninsuffizienz beschränkt. Obwohl Organe von älteren Spendern bekannterweise kürzere Überlebensraten aufweisen, nimmt die Zurückhaltung bei der Verwendung solcher Organen mit zunehmender Erfahrung und Nachfrage ab. Gleichzeitig mit der zunehmenden Zahl von älteren Patienten auf der Warteliste für eine Nierentransplantation steigt das Interesse an der Entwicklung von speziellen Allokations-Strategien für diese Patienten. Basierend auf dem Konzept der Abstimmung des metabolischen Bedarfs des älteren Empfängers und der Kapazität der älteren Spenderniere entwickelte Eurotransplant daher das Eurotransplant Senior Program (ESP), welches im Januar 1999 gestartet wurde. Im Rahmen dieses Programms werden Nieren von über 65 Jahre alten Spendern auf eine selektierte Gruppe über 65 Jahre alter Empfänger übertragen, die nicht- immunisiert sind und ihr erstes Transplantat erhalten. Das Ziel dieser 5-Jahres Analyse war es herauszufinden, ob das ESP erfolgreich seine Ziele erreicht hat, Organe von älteren Spendern optimal zu nutzen und die Zeit auf der Warteliste für ältere Empfänger zu verkürzen. Als Basis dienten Daten des Eurotransplant Information Systems (ENIS). Zusätzliche Informationen wurden erfolgreich für mehr als 80% der ESP Patienten sowie für zwei verschiedene Kontrollgruppen mit demselben Beobachtungszeitraum und entweder annähernd vergleichbarem Alter des Spenders (Kontrolle 1) oder des Empfängers (Kontrolle 2) erfasst. Insgesamt zeigt diese Auswertung, dass die Ziele des ESP erreicht wurden. Die Verfügbarkeit von älteren Spenderorganen wurde von 162 (10%) im Jahre 1998 auf 239 (fast 15%) im Jahre 2004 gesteigert. Die Wartezeit für ältere Empfänger verkürzte sich signifikant im Vergleich zu vor der Einführung des ESP und weiter im Verlauf der ersten 5 Jahre auf deutlich unter 4 Jahre. Im Gegensatz dazu verlängerte sich die Wartezeit für Patienten in den Kontrollen die über ETKAS transplantiert wurden um bis zu einem Jahr. Die kalte Ischämiezeit für ESP Patienten war signifikant kürzer mit etwa 12 Stunden im Vergleich zu ca. 17 Stunden für Patienten der Kontrollgruppen. Unter Berücksichtigung der Tatsache, dass die Kontrollgruppen sich hinsichtlich Spender und Empfängeralter teils deutlich von der ESP Gruppe

unterschieden, sind die wesentlichen Ergebnisse, insbesondere das Patienten- und Transplantatüberleben der ESP Gruppe nicht negativ beeinflusst. ESP Patienten hatten jedoch deutlich mehr Abstoßungsreaktionen. Die Analyse der unabhängigen Risikofaktoren für akute Abstoßungsreaktionen weist darauf hin, dass ein verbessertes HLA matching unter Beibehaltung kurzer Ischämiezeiten möglicherweise von Vorteil wäre.

Abstract (English)

The ever increasing proportion of elderly individuals in our society and the shortage of organs impose significant challenges to organ transplantation. As a result, organs previously considered marginal are now routinely used. Although increased donor age is associated with reduced graft survival rates, the changing trends in donor profiles have forced the transplant community to use organs from elderly donors. At the same time, an increase in the number of elderly patients on renal transplant waiting lists has heightened interest in the development of special allocation strategies for these patients. As a result, Eurotransplant started the Eurotransplant Senior Program (ESP) in January 1999, an allocation scheme based on the concept of matching the metabolic demand of the recipient and the excretory capacity of the donor. The program obtained kidneys from donors older than 65 years and allocated them to a selected group of patients in the same age group who were non-immunized and were receiving their first transplant. The main objective of this evaluation of the ESP 5 years after its initiation was to find out if the allocation scheme is effective in using kidneys from elderly donors and if it shortens the waiting time for elderly patients requiring kidney transplantation. The Eurotransplant database was used as a starting point, and data added to the database by collecting additional information on more than 80% of the ESP patients, and on two control groups. The controls were observed over the same time period as the ESP patients, and matched the ESP patients for donor age (Control 1) and the recipient age (Control 2). Overall, this 5-year analysis of the ESP shows that the objectives of the program have been met. The availability of elderly donors increased from 169 (10%) in 1998 to 239 (almost 15%) in 2004. The waiting time for elderly recipients transplanted within the ESP was successfully reduced compared to the waiting time before introduction of ESP and is now below 4 years, while waiting time in both control groups has increased by up to one year. The cold ischemia time for ESP

patients was significantly shorter, with a mean of approximately 12 hours compared with over 17 hours in both control groups. After correcting for the differences in the control groups of either donor or recipient age compared to the ESP group it was demonstrated that the main clinical outcomes in recipients of organs from donors age 65 or older were not negatively impacted by the ESP allocation. However, ESP patients experienced significantly higher rates of acute rejection. Based on an analysis of independent risk factors the use of HLA matching instead of waiting time should be considered as an allocation criterion while maintaining a short cold ischemia time.

List of abbreviations-

AE	Adverse Event
ANOVA	ANalysis Of VAriance
AR	Acute Rejection
BL	Baseline
CNI	CalciNeurin Inhibitor
CIT	Cold Ischemia Time
CL	Confidence Limit
CrCl	Creatinine Clearance
CV	CardioVascular
DGF	Delayed Graft Function
DSO	Deutsche Stiftung Organtransplantation
DwFG	Death with Functioning Graft
ECD	Expanded Donor Criteria
ENIS	Eurotransplant Network Information. System
ESP	Eurotransplant Senior Program
ESRD	End Stage Renal Disease
ETKAS	EuroTransplant Kidney Allocation System
GFR	Glomerular Filtration Rate
HLA	Human Leukocyte Antigen
IL	Interleukin
IS	Immunosuppression, immunosuppressive
max	maximum
med	medium
min	minimum, minutes (depending on context)
MMF	Mycophenolate Mofetil
NA	Not Applicable
OPTN	Organ Procurement and Transplantation Network
PRA	Panel-reactive antibody
Q1	First quartile
Q3	Third quartile
RR	Relative Risk

SAE	Serious Adverse Event
SCr	Serum Creatinine
SAP	Statistical Analysis Plan
SD	Standard deviation
SRTR	Scientific Registry of Transplant Recipients
Tx	Transplantation
UNOS	United Network of Organ Sharing
USRDS	United States Renal Data System
WL	Waiting List

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1   Background and Rationale

1.1   Background

The life expectancy of the population in general is increasing consistently, as is the age of the dialysis population. Consequently, donors and recipients are getting older, and renal transplantation has become a therapy that is not limited to the youngest segment of patients with terminal renal failure. Reluctance to use organs from elderly subjects has decreased with increasing discrepancy between the number of available donors and demand. Reluctance to put elderly patients on the waiting list still seems high, with a median age of patients on dialysis in Germany being 64 years but the median age of transplant patients being 49 years (http://www.quasi-niere.de). There are several likely reasons, including the fact that worse short-term and long-term outcomes have been reported for older recipients and as a result of the donor shortage younger patients are often given priority.

Despite expanding knowledge and experience with aging donors and recipients, numerous questions remain unanswered or controversial.
Amongst others, the main questions relate to:

- the effect of donor age on outcome after renal transplantation
- the effect of recipient age on outcome after renal transplantation
- adapting immunosuppressive therapy for elderly recipients
- the effect of age matching on outcome after renal transplantation

These questions will be addressed in the following sections, followed by a brief introduction to the Eurotransplant Senior Program and its analyses to date.

1.1.1   The effect of donor age on outcome after renal transplantation

Due to excessive waiting times of about 5 years or longer (source: http://www.quasiniere.de, http://www.optn.org) and the increasing disparity between organ supply and demand, the use of kidneys from "marginal donors" or "expanded criteria donors" (ECDs) - with older age being one of the criteria - has become generally accepted and increasingly common (Metzger, et al., 2002). In the past decade, the proportion of deceased donors in the US older than 50 years of age has increased from 21% to over 30% with an increase in donors aged 65 and above from 4,2% in 1994 to

7,4% in 2004 (source: http://www.optn.org). Eurotransplant data also show an increased usage of elderly donor kidneys in recent years with more than 14% of donors in 2003 being over 65 years old (Cohen 2004). In Germany ,this proportion is even higher at 20% (Figure 1; Source: DSO, http://www.dso.de).
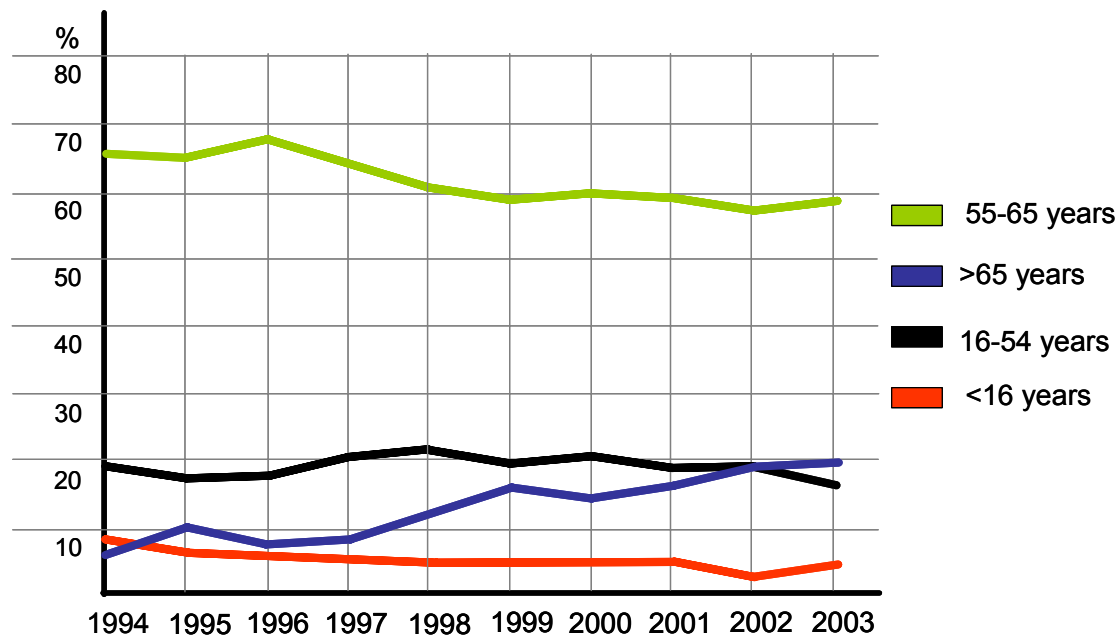
Figure 1: Transplants in Germany by donor age (Source: DSO, http://www.dso.de)

Results documenting evidence of an inferior outcome of grafts from elderly donors were already published in 1974 (Darmady, 1974). In the early postoperative period, an increased rate of primary non-function and delayed graft function was reported, both of which are well-known risk factors for allograft survival in general (Cecka, et al., 1992; Sautner, et al., 1991). The impact on long-term outcome, however, was even more dramatic. In 1994, Alexander and co-workers reported the two-year transplant survival with regard to donor age in more than 30,000 transplantations performed between 1987 and 1991 (Alexander, et al., 1994) . When adjusted for various covariates (number of previous transplants, donor and recipient race, presence of diabetes mellitus, percentage of panel-reactive antibodies (PRA), cold ischemia time and HLA mismatch), the lowest risk for graft failure at one year was seen in kidneys obtained from donors aged 16-45 years. With each decade of increase in donor age, the relative risk rose by 15%-20%. The magnitude of this effect, however, increased exponentially with time, reaching an odds ratio for failure after two years of 3.25 with donors older than 70 years, compared with a group of 30-year-old donors. Terasaki reported a higher

prevalence of delayed graft function, an increased need for postoperative dialysis, higher serum creatinine at discharge and higher acute rejection rates in recipients from older donor kidneys. The projected transplant half-life decreased from 10.2 years if the donor was 16-20 years old to 5 years for grafts retrieved from donors who were 60 years of age or older (Terasaki, et al., 1997). A particularly striking effect of donor age on long-term outcome was described by Gjertson in 1996 (Gjertson, 1996): in grafts surviving the first postoperative year, donor age accounted for 30% of the variability in outcome, the effect at one year was also significant, but at 4.1% much less striking. In an analysis by Nickerson et al., the adjusted odds ratio for an increase in serum creatinine of more than 20 µmol/L 6 to 24 months post-transplantation was 1.09 for every year increase in donor age (Nickerson, et al., 1998), and an analysis of the USRDS database published in 2005 confirmed that initial GFR at 6 months but also stability of GFR in the first year were significantly lower among recipients of donors > 55 years (Woo, et al., 2005).

Organs from elderly donors seem to be particularly susceptible to ischemia-reperfusion injury leading to increased rates of DGF. Ojo reported a 23% increase in DGF for every 6 hours of cold ischemia in transplant recipients of any age, consequently leading to higher risk of acute and chronic rejection (Ojo, et al., 1997). This effect seems to be even more pronounced with increasing donor age and has been found as an independent risk factor for chronic graft deterioration (Shoskes and Cecka, 1998; Tullius, et al., 2000).

As a matter of concern, donor age has recently been shown to represent a significant risk factor for patient death with functioning graft (Meier-Kriesche, et al., 2002). The author speculates that the poor function of the aged graft could lead to hypertension and increased incidence of cardiovascular events.

Even with live donors some (Langle, et al., 1992; Matas, et al., 2000), but not all (Matas, et al., 1976), authors have argued that donor age determines long-term outcome.

In summary, donor age has been shown to have an impact on the incidence of DGF, graft function, graft survival and patient death with functioning graft and has thus turned out to be a powerful predictor of long-term outcomes after renal transplantation.

1.1.1.1 Age related changes in the graft

Inferior outcomes in patients receiving an organ from an older donor might be related to changes in the donor organ as a result of the aging process. The biologic price of aging includes progressive deterioration of renal function and structure (Anderson and Brenner, 1986). Histopathological studies reveal a 20% to 25% loss of volume, particularly in cortex, fibrous intimal thickening of arteries, loss of glomeruli due to sclerosis with enlargement of the remaining glomeruli, patchy tubular atrophy and interstitial fibrosis in aging kidneys (Goyal, 1982). Kumar et al. performed pretransplant biopsies of kidneys from donors older than 55 years. Age-associated glomerulosclerosis was present in 85%, patchy interstitial fibrosis in 64%, thickening of the arteriolar wall and mesangium in 47%, chronic inflammatory cells in the interstitium in 29% and cystic changes in 6% of the kidneys (Kumar, et al., 1993). However, a clear correlation of age-associated changes in pre-transplant biopsies with postoperative function has not been shown, and association between function and donor age in individual cases is very weak. This is not completely surprising. The Baltimore Longitudinal Study of Aging showed that one-third of the participants did not evidence any change in glomerular filtration rate (GFR) over time (Lindeman, et al., 1985). Epstein concluded that the common denominator for the functional changes occurring with aging is more a diminution in the kidney's ability to respond appropriately to the challenges of either deficits or excesses. These alterations attain clinical significance only when renal function is challenged by superposition of co-morbid conditions like hypertension or heart failure (Epstein, 1996; Fliser, et al., 1997; Fliser and Ritz, 1998). Not surprisingly therefore, the medical history of the donor provides information about the expected post transplant course independent of donor age. Kidneys from patients dying of cardiovascular events or stroke fail more often than do organs from donors dying of subarachnoidal haemorrhage (Troppmann, et al., 1991). Analyses of allografts from donors >55 years with a history of long-term arterial hypertension reported to UNOS showed decreased long-term function (Carter, et al., 2000). Ojo et al. report similar findings not only for pre-existing donor hypertension but also for diabetes, exerting only a modest, yet significant, negative effect on several transplant outcomes (Ojo, et al., 2000).

The postulate of an increased sensitivity of grafts from marginal donors towards additional injuries has nicely been illustrated by Tullius et al. (Tullius, et al., 2001)

(Figure 2). Grafts from marginal donors may be particularly sensitive toward additional alloantigen-specific and -unspecific injuries before and after transplantation. The quality of the graft is influenced by various risk factors including donor age, previous diseases, and consequences of brain death. Further perioperative damage resulting from operative manipulations during the harvesting procedure and consequences of ischemia/reperfusion injury may damage grafts from marginal donors more than those from optimal donors. After transplantation, alloantigen specific and unspecific changes, acute rejection episodes, T cell activating processes, viral infections and drug toxicity may have a stronger impact on marginal grafts with the consequence of reduced long-term function.
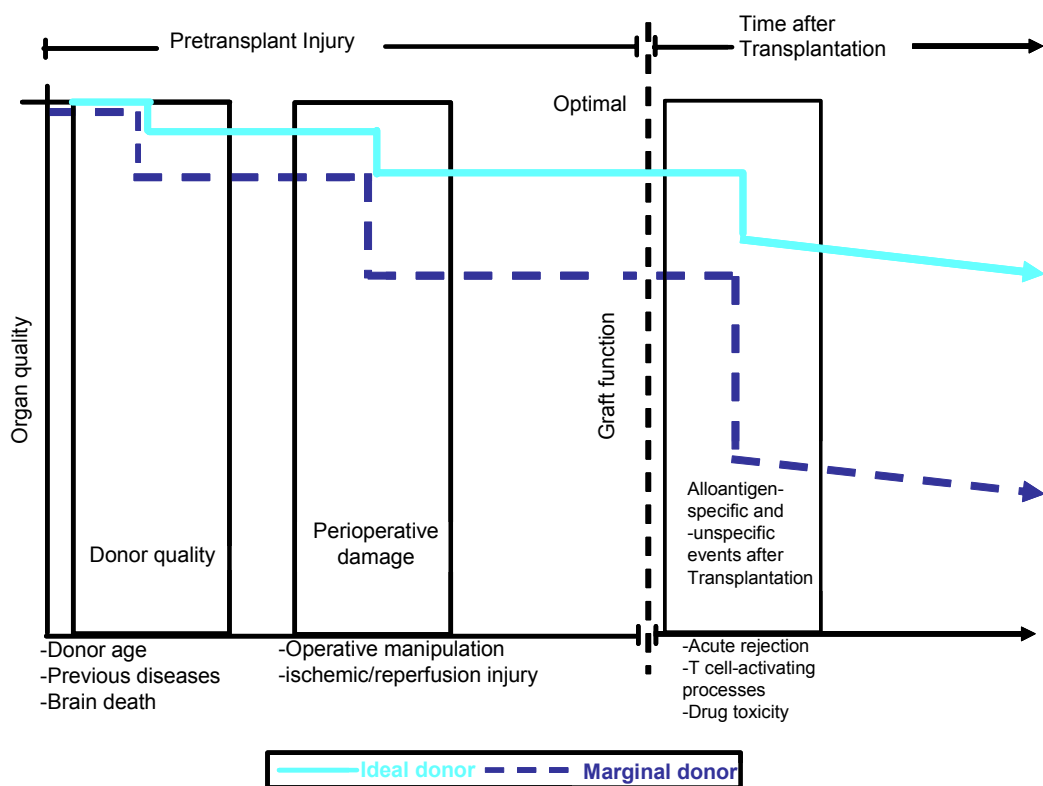
Figure 2: The postulate of an increased sensitivity of grafts from marginal donors towards additional injuries (Tullius, et al., 2001)

Ideally, what the transplant community would need is a measure for organ damage to predict the outcome of grafts from elderly donors. Creatinine clearance and biopsies have been tested for their predictive value; although creatinine clearance was determined as the optimal predictor of graft survival (Kerr, et al., 1999), others suggested a glomerulosclerosis index or the degree of fibrous intimal thickening at the time of implantation (Andres, et al., 2000) (Bosmans, et al., 2000). Singh et al. analyzed existing scoring systems and concluded that a donor CrCl of ≥70ml/min is a better

discriminator than a donor CrCl of 90ml/min and comparable to the Nyberg variables (cold ischemia time, donor diabetes and hypertension; incremental donor age and cause of death) (Singh, et al., 2004).

1.1.2 The effect of recipient age on outcome after renal transplantation

In general, advanced recipient age is no longer a contraindication for renal transplantation. In the Eurotransplant area the number of renal recipients in the age category >65 years has more than doubled in the past ten years. The average number of recipients in the age group 60-65 increased by 37% from 1999 to 2003 as compared to the period from 1994-1998. In 2003, 10.8% of all transplantations reported to the Eurotransplant registry were performed in recipients older than 65 years (Cohen, et al., 2005). In the US Renal Data System, the percentage of renal transplant recipients ≥65 years of age also increased from 4.9% to 11.6% between 1994 and 2004 [Source: http://www.optn.org].

1.1.2.1 Mortality compared to patients on the waiting list

While older end stage renal disease (ESRD) patients on the waiting list have a 5 times greater likelihood of dying compared to patients less than 50 years (Smits, et al., 2002), transplantation has been shown to improve long term survival even in the higher age groups (Wolfe, et al., 1999).

The long term mortality risk for transplant recipients was estimated to be 68 percent lower than that for patients on the waiting list. Figure 3 shows the relative risk of death among 23,275 kidney transplant recipients compared to patients on dialysis. The risk of death during the first 2 weeks after transplantation is 2.8 times higher than for patients on dialysis, and remains elevated until 106 days post-transplant. After this time, this risk was lower among transplant recipients with the likelihood of survival becoming equal at day 244.   Analyses for the different age groups showed that an early benefit and the greatest difference in long-term survival was found among patients who were 20-39 years old with equal risk of death after 11 days, likelihood of survival being equal after 57 days and a projected increase in life expectancy of 17 years. Among the patients who were 60-74 years old, the cumulative survival rate improved after the first year, with a projected increased life span of five years and a decrease in the long term risk of death of 61 percent (Wolfe, et al., 1999) (Table 1).
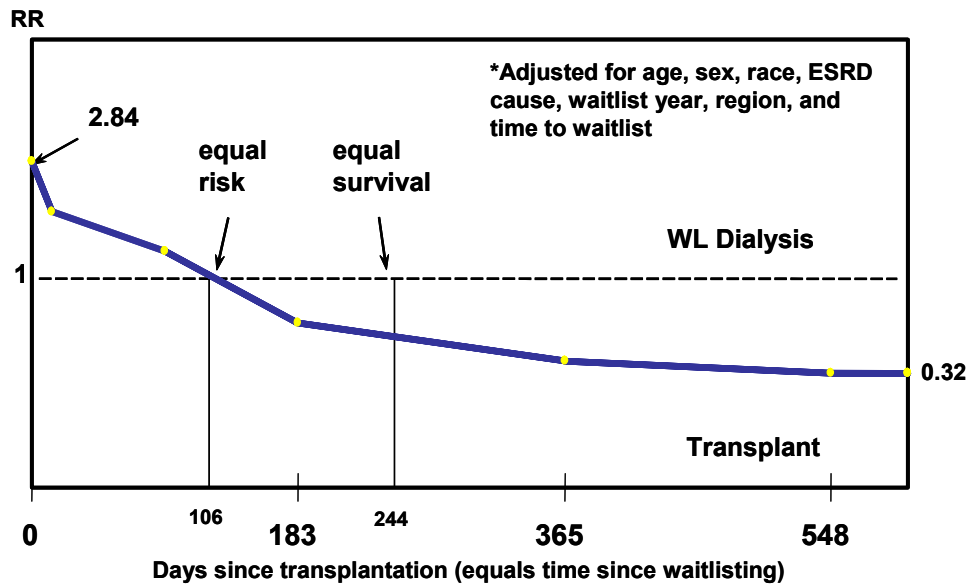
Figure 3: Mortality RR for 23,275 First Cadaveric Transplant vs. 46,164 Waitlisted Dialysis Patients*(Wolfe, et al., 1999)

Table 1: Transplant vs. wait-listed dialysis patient survival for different age groups, 1991-1997(Wolfe, et al., 1999)

Age at WL	Annual % Dead WL	RR long term	Days to Equal		Lifetime* WL (yrs)	Extra Lifetime* Tx (yrs)
			Risk	Survival		
All	6.3	0.32	106	244	10	+10
0-19	2.2	0.33	3	5	26	+13
20-39	4.3	0.24	11	57	14	+17
40-59	6.5	0.33	94	255	11	+11
60-74	10.0	0.39	143	369	6	+5

1.1.2.2 Graft survival

Clearly, graft loss due to death is more common in the elderly, occurring at a rate of 1.1/100 patient years in recipients aged 18-49 and at 4.1/100 patient years in recipients older than 65 years (Meier-Kriesche, et al., 2000)

Contradictory results for death-censored graft survival have been published. In a study by Roodnat et al., the overall relative risk for allograft failure increased by only 1.44% for each year of recipient age (Roodnat, et al., 1999), even though patient survival decreased by 5% per year. Tesi et al. reported a five-year patient survival rate of 68.1% in elderly but 89.1% in younger recipients. Death-censored graft survival, on the contrary, was 11% better in the older group, so that crude graft survival was almost identical (Tesi, et al., 1994). In a large analysis by Gjertson one-year graft survival was 84.2% in recipients older than 65 years and 87.3 % in the age group 43-65 years. Uncensored five-year graft survival was 69.4% and 72.5%, respectively. These differences, although statistically significant, are quite small in absolute terms, and age accounted for only 2.1% of the variance in five year graft outcome (Gjertson, 1996).

Recent data, however, indicate that elderly recipients might be more prone to developing chronic allograft nephropathy and consequent graft loss. Using data from the USRDS, Meier Kriesche et al. demonstrated that eight-year death-censored graft survival is significantly decreased in the older age groups, being 67% for ages 18-49 vs. 62% for ages 50-64 and 51% for ages 65+. In multivariate analysis recipient age was a strong and independent risk factor for chronic allograft failure in Caucasians. These findings were reinforced by an analysis that was restricted to living donor transplants without rejection (Meier-Kriesche, et al., 2002). It has been argued that age-related factors, like increased concentrations of transforming growth factor beta or lipoproteins in the serum, might contribute to accelerated senescence of the graft (Meier-Kriesche, et al., 2002) (Janssen, et al., 1998) (Nakamura, et al., 1999)(see also 1.1.2.6.).

1.1.2.3 Immune response and rejection

Conflicting data have been published regarding the impact of recipient age on the incidence of acute rejection. While Meier-Kriesche (see also Figure 5), Ismail, Hestin and Jassal report lower rejection rates according to the concept of a global deterioration of the aging immune system, other publications report a normal or even higher risk of acute rejection in the group of elderly kidney transplant recipients, e.g. De Fijter, Waiser, Schratzberger, Morris and Moreso (de Fijter, et al., 2001; Moreso, et al., 1999; Morris, et al., 1999; Schratzberger and Mayer, 2003; Waiser, et al., 2000). However, recent clinical trials with calcineurin inhibitor-free immunosuppressive regimens demonstrated a high incidence of acute rejection episodes in elderly recipients,

particularly in the early post transplant period, leading to a conversion of immunosuppression in the majority of patients in this group (Kasiske, et al., 2000). The initial reports from the ESP also show higher than expected rates of acute rejection. The reduced incidence of acute rejection episodes may not apply, especially when grafts from older donors are allocated to elderly recipients. This will be further discussed in section 1.1.6.

1.1.2.4 Infectious complications in the elderly

Infections in the elderly occur more frequently and more severely, and have distinct features with respect to clinical presentation, laboratory results, microbial epidemiology, treatment, and infection control (Gavazzi and Krause, 2002). The reduced resistance to infection in the elderly is further compromised by immunosuppression, making this group particularly susceptible to opportunistic infections. In 2001 Meier-Kriesche showed that death related to infections during the first 24 months increased progressively whereas the incidence of acute rejection during the first 6 months decreases in transplant recipients with increasing age. In the highest age group the relative risk of death due to infection is increased by more than 6 times (Meier-Kriesche, et al., 2001) (Figure 5).
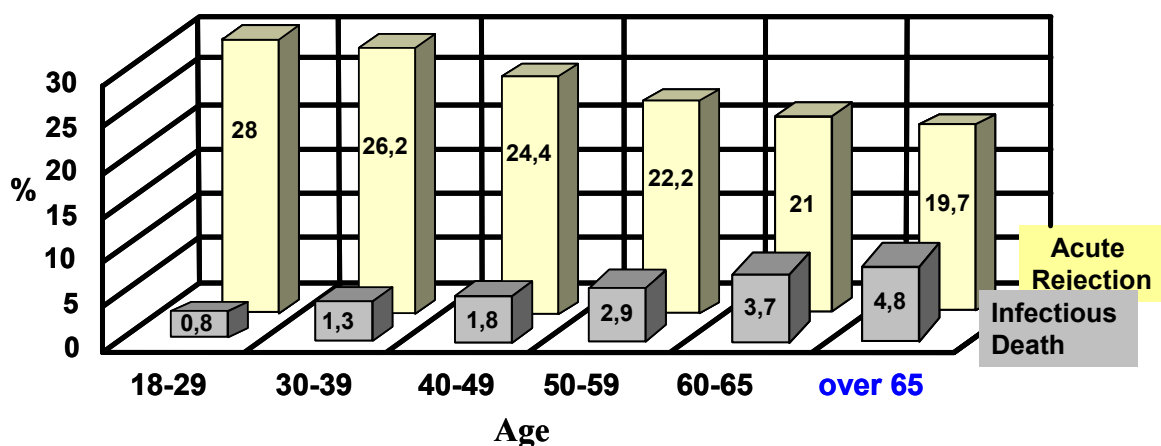

Figure 4: Incidence of infectious death during the first 24 months versus acute rejection in the first 6 months with increasing age (Meier-Kriesche, et al., 2001).

1.1.2.5 Other age related non-immunologic changes

The incidence of most cancers also increases with age. There is concern that elderly transplant recipients on immunosuppression are particularly at risk for malignancies. Indeed, it has been reported that the mortality related to cancer in patients aged more than 65 years is 7.1 per 1000 patients compared with 2 per 1000 patients in patients aged less than 40-49 years (Meier-Kriesche, et al., 2001). Age related non-immunologic changes also include co-morbidities such as cardiovascular disease and hypertension but also lipid disorders and diabetes. Cardiovascular disease plays an increasing role with age (Kasiske, 2001) and pre-existing long-term hypertension of the recipient is considered a risk factor (Frei, et al., 1995). It has also been shown that increased concentrations of homocysteine, apolipoproteins, and altered insulin-like growth factors accelerate progression of arteriosclerosis in the elderly (Meier-Kriesche, et al., 2000).

1.1.2.6 Immunologic changes in the recipient

It is widely accepted that the immune system, and thus the immune response, become impaired with age (Wick and Grubeck-Loebenstein, 1997). The most relevant age-related immunologic modifications are related to T-cells, because they play a pivotal role in rejection and tolerance. Many studies have demonstrated the functional and phenotypic changes in T lymphocytes with age (less proliferation, shortening of telomeres, IL-2 secretion etc) theoretically leading to a cellular and humoral immunodeficiency in the elderly. Consequently, the incidence and severity of acute rejections in elderly recipients would be expected to be lower compared to younger recipients, providing an argument to support the concept of age-matching in renal transplantation.

However, there is some controversy on the decrease of total lymphocytes with aging vs. alteration of certain cell-subsets (Lehtonen, et al., 1990). Important changes in the immune system that may increase the incidence of chronic rejection include increased numbers of memory T cells, low CD4/CD8 ratio, T helpers 1 and 2 shift with increased pro inflammatory cytokines (tumour necrosis factor-α, interleukin [IL]-4, interferon-γ, transforming growth factor-β-1, and IL-6) (Meier-Kriesche, et al., 2000; Sandmand, et al., 2002), increased antigen-presenting cell activation (Castle, et al., 1999; Sidman, et

al., 1987; Verbeke, et al., 2001), up-regulation of HLA-DR (Rea, et al., 1999), and production of anti-donor HLA antibodies (Paul, 1997; Smith, et al., 2000) supporting the findings of an increased rate of antibody mediated rejection (de Fijter, 2005; de Fijter, et al., 2001). IL-4 may play an important role in the development of transplant arteriosclerosis by stimulation of vascular smooth muscle cell proliferation (Bagley, et al., 2000).

1.1.3 Immunosuppressive therapy for the elderly

 As discussed above, elderly renal transplant recipients have both a higher incidence of patient death and allograft loss censored for death. Acute rejections are less frequent in older individuals; however this might not apply when grafts from older donors are allocated to elderly recipients and the consequence of a rejection, if it occurs, is negative for long-term graft survival. On the other hand, death by infection is exponentially increased in older versus younger renal transplant recipients. In general, the pharmacokinetics of the immunosuppressive agents are little affected by age, but the tolerance to these agents seems to decrease with increasing age.

Although there are some regimens recommended by single-centre studies, widely accepted immunosuppressive protocols specific to the elderly are not available.

Despite the fact that elderly transplant recipients appear to have a decreased risk of acute rejection, they have an independently increased risk of chronic allograft loss (Meier-Kriesche, et al., 2000). Part of this increased risk of chronic allograft nephropathy may be explained by an increased susceptibility to calcineurin inhibitor related nephrotoxicity. For this reason, protocols that avoid, minimize or <u>delay the introduction of calcineurin inhibitor</u> have been used for older recipients, and these suggest that minimization of these drugs is generally accompanied by improved renal function, especially when receiving a graft from an older donor (Arbogast, et al., 2005; Theodorakis, et al., 2000). A group from Munich reported long-term results of 89 patients on a CNI-free, MMF-based immunosuppressive protocol in elderly recipients of kidneys from elderly cadaver donors. They showed a cumulative 5-year patient and renal allograft survival of 87.69% and 69.81%, outcomes which are comparable with data from young recipients who have received allografts from young cadaver donors (Arbogast, et al., 2005).

A recent analysis of more than 5,000 patients from the SRTR database indicated that in elderly renal transplant recipients, MMF is associated with lower early and late rejection rates as compared to Azathioprine and is associated with a significantly higher rate of patient survival 4 years post-transplantation (Meier-Kriesche, et al., 2004).

Induction therapies with antilymphocyte agents (antilymphocyteglobulin, antithymocyte globulin, and OKT3) do not seem appropriate for the elderly because they have been associated with a high incidence of infections and malignancies (Lundgren, et al., 1985). IL-2 receptor antibodies in the elderly seem promising but require further assessment (Pascual, et al., 2002). A retrospective data analysis on 183 kidney transplant recipients ≥60 years of age compared four consecutive cohorts of kidney transplant recipients receiving lymphocyte immune globulin, equine antithymocyte globulin [n = 29]; muromonab CD3 [n = 45]; IL-2 receptor antibody with [n = 40] and without (n = 69) corticosteroid maintenance. Patients with IL-2 receptor antibody induction had significantly lower rates of DGF and acute rejection, were free of adverse effects typically encountered by patients receiving polyclonal and monoclonal antibodies and had much shorter hospital stays (Heifets, et al., 2004).

In summary, tailoring the immunosuppressive regime to take into account the altered immune response and increased risk of drug toxicity, infections, cardiovascular disease and changes associated with advanced age seems to be the best strategy to improve the survival and quality of life in the elderly transplant population.

1.1.4   The effect of age matching on outcome after renal transplantation

The idea of age-matching has a long history and is based on the concept of "functional matching" between the decreasing metabolic demand of the recipient and with the reduced functional reserve of the elderly graft (Anderson and Brenner, 1986; Donnelly, et al., 1990; Gjertson, et al., 1997; Kuo, et al., 1996; Smits, et al., 1998), and is also based on the logical and fair principle that the shorter half-life of elderly organs meets the short life expectancy of elderly recipients. In addition, some believe that a corresponding age of donor and recipient may provide a better "immunologic matching" (Cecka and Terasaki, 1995; de Fijter, et al., 2001; Tesi, et al., 1994; Waiser, et al., 2000).

Analysis of clinical studies on the effects of age matching has shown conflicting data. In 1991, Donnelly et al. published their results of 141 consecutive first cadaveric

transplants and noted that graft failure at two years was significantly greater when the donor was more than five years older than the recipient (Donnelly, et al., 1991). Subsequent studies were unable to replicate these findings, but the number of patients involved was quite low (Newstead and Dyer, 1992; Pirsch, et al., 1992).

Alexander et al. reported lower allograft survival of elderly kidneys when transplanted into elderly recipients, but the impact of donor age and recipient age on the risk of graft failure was independent. In 1995, Cecka and Teresaki repeated this analysis of the UNOS registry data and identified 1740 kidneys from donors over the age of 60 among 45922 cadaver transplants performed between October 1987 and March 1994. Actuarial graft survival (not censored for patient death) was significantly worse at one and especially at ten years in these kidneys, as compared to donors aged 19-30 years (70% vs. 84% at one year and 20% vs. 45% at ten years). Data censored for patient death, however, revealed the best survival of elderly kidneys in elderly recipients (one-year graft survival 78%, projected ten-year graft survival 43% as compared to 70% at one year and 22% projected ten-year graft survival in recipients aged 19 and 45 years). Moreover, at one year, serum creatinine tended to be lower in age matched elderly grafts. In another retrospective study analyzing various age allocations, the combination of a young recipient with an old donor provided a poor outcome (20.8% graft survival by 8 years), whereas old-to-old matches obtained the best long-term results (57.1% death-censored graft survival by 8 years) (Waiser, et al., 2000) (Figure 5).
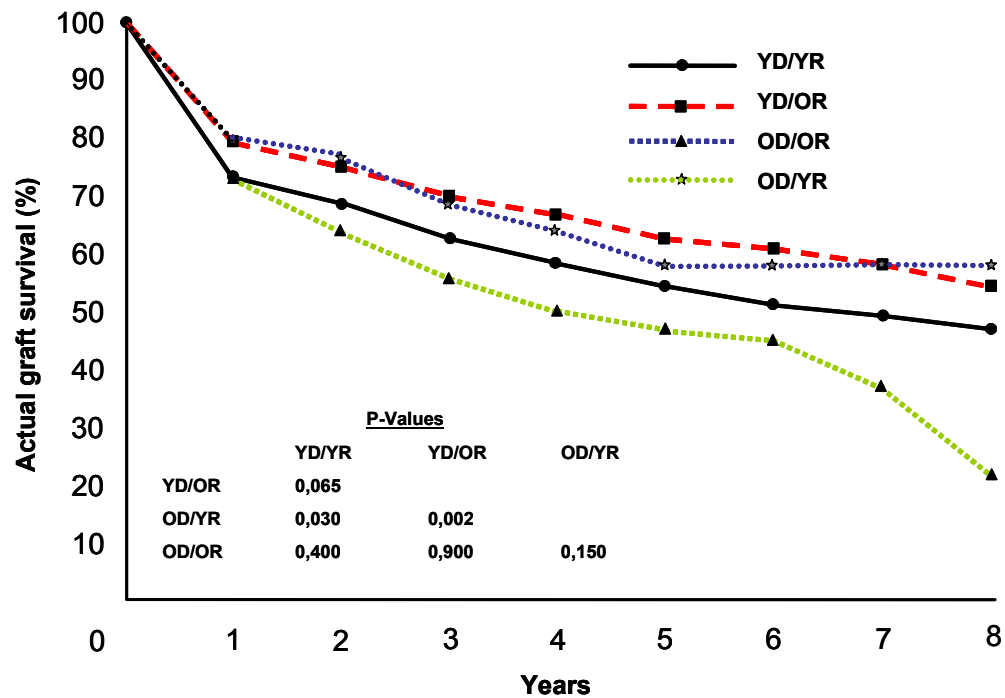
Figure 5: The influence of age-match on actual (death censored) graft survival (Kaplan-Meier plot with a log-rank test)(Waiser, et al., 2000)

YD, young donors (<55 years); OD, old donors (>55 years); YR, young recipients (<55 years); OR, old recipients (>55 years)

In contrast, other studies demonstrated no or only marginal beneficial effect of age matching (Kasiske and Snyder, 2002) or even reported a synergistic deleterious effect on renal allograft survival for the interaction of donor and recipient age (Meier-Kriesche, et al., 2002) (Figure 6).
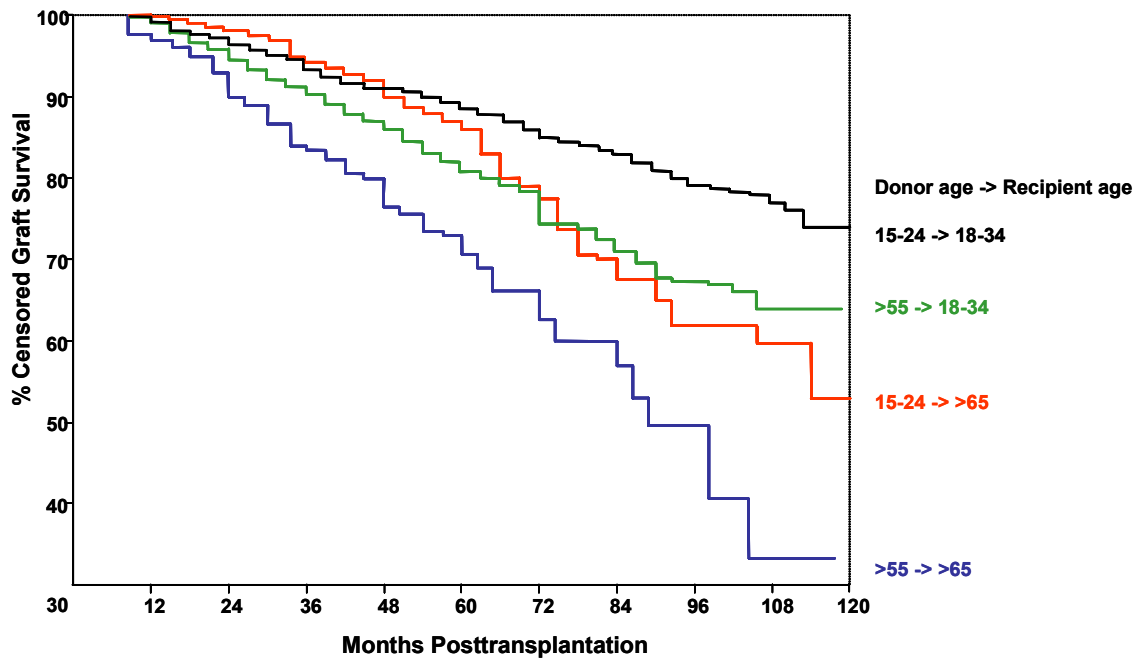
Figure 6: Death-censored graft survival beyond 6 months post-transplantation for different age matched groups (Meier-Kriesche, et al., 2002)

It is important to mention that these analyses were not intended to address issues of allocation or draw conclusions about age-matching programs that also have to take ethical and economic considerations into account.

1.1.5 Eurotransplant and the Eurotransplant Senior Program

The Eurotransplant International Foundation is responsible for the mediation and allocation of organ donation procedures in Austria, Belgium, Germany, Luxemburg, the Netherlands and Slovenia. In this international collaborative framework, the participants include all transplant hospitals, tissue-typing laboratories and hospitals where organ donations take place. The Eurotransplant region numbers well over 118 million inhabitants.

The Eurotransplant Senior Program (ESP) is a natural response to the universal trend of extending donor criteria. The program obtains kidneys from donors older than 65 years and allocates them to a selected group of patients in the same age group with the aim of: (i) achieving a more efficient use of kidneys from elderly donors; and (ii) increasing the rate of transplantation in elderly patients. The rationale for the recipient age restriction is that a kidney graft that outlives the recipient is considered a success. If

donor organs are physiologically slightly suboptimal, as is more likely with older donors, the graft has a greater chance of surviving an older than a younger recipient.

Thus, Eurotransplant developed the ESP, an allocation scheme based on the concept of matching between metabolic demand of the graft recipient and excretory capacity of the donor organ. The rationale for a donor and recipient age matching policy in which a kidney graft should outlive the recipient implied that HLA matching could be disregarded in assigning donor organs.

However, the use of organs from elderly donors is often accompanied by increased incidences of delayed graft function and rejection. To improve the chance of success, defined as graft viability, strict rules for participating centres within the Eurotransplant region were imposed: (i) to reduce ischemic damage, kidneys should be transplanted with the shortest possible cold ischemia time; and (ii) to reduce immunological risk, only non-immunized [i.e. panel-reactive antibody (PRA) <5%] first transplant recipients were included. The ESP allocation scheme furthermore included the option of transplanting both kidneys to a single recipient in cases in which the donor creatinine clearance was <70 ml/min.

Tailor-made allocation schemes like ESP are designed by Eurotransplant and offered thereafter to the Eurotransplant community. Thus, treating physicians in individual centres have the responsibility to carry out the details of the programme and to obtain informed consent from their patients.

The idea of ESP was conceptualized by the Eurotransplant Kidney Advisory Committee in 1998 and finally approved by the Eurotransplant-Board as well as by the Ständige Kommission Transplantation der Bundesärztekammer. The program was implemented in January 1999. For the first two years (4 January 1999 to 4 January 2001), participation of the centres was on a voluntary basis. As of 4 January 2001, the ESP became part of the ETKAS (Smits, et al., 2002).

1.1.6 ESP analyses to date

Evaluations of the ESP program have been scarce to date and limited by short follow-up and/or the use of different or historical controls. Out of 8 reports, 2 have been published by ET comprising topline results of the entire ESP population, the remaining 6 are single centre analyses with 3* of them at least partially reporting results of the same patient population. The table below gives an overview of the publications to date, the number of ESP patients included in each analysis and the duration of follow-up.

Table 2: Overview of published analyses of the ESP to date

Reference	Number of ESP patients	Years after start of ESP (mean FU)
Cohen et al 2005, Expanding the donor pool to increase renal transplantation (Cohen, et al., 2005).	876	3 years
Giessing et al 2004, Kidney donors and kidney transplantation in the elderly (Giessing, et al., 2004)*	68	5 year (23,3 mo)
Giessing et al 2004, "Old-for-old" cadaveric renal transplantation: surgical findings, perioperative complications and outcome (Giessing, et al., 2003)*	26	3 years
Fritsche at al.2003, Old-for-old kidney allocation allows successful expansion of the donor and recipient pool.(Fritsche, et al., 2003)*	69	4 years (18,1 mo)
Krüger at al 2002, Early experience with the ET Senior Program "Old For Old"; better to be number one?(Kruger, et al., 2002)	14	18 months (3 mo)
Smits at al. 2002, Evaluation of the Eurotransplant Senior Program. The results of the first year.(Smits, et al., 2002)	227	1 year
Schlieper at al 2001, Eurotransplant Senior Program 'old for old': results from 10 patients.(Schlieper, et al., 2001)	10	9 months (4 mo)
Beckurts at al. 2001, Single-center experience with the "Old for Old" program for renal transplantation.(Beckurts, et al., 2001)	20	24 mo (21 mo)

The results of the first year of the ESP program were published by Jaqueline Smits et al. in 2002. The analysis of 227 transplants demonstrated that 1-year graft survival rates censored for graft loss because of death were 86% compared with 79% when old grafts were allocated through the normal system Eurotransplant Kidney Allocation System (ETKAS) to recipients of any age. Median cold ischemia time was shorter in the

ESP program (12 vs. 19 hours), while the number of HLA mismatches was significantly higher (4 vs. 2). Institution of ESP in participating centres doubled the number of organs harvested from donors older than 65 years, and the discard rate dropped from 22% to 13%. Median waiting time for recipients older than 65 years decreased within a year from 943 to 707 days, and the number of patients on the waiting list also decreased significantly from 905 to 872. There was no difference between the study groups with regard to initial transplant function or graft function at one year (censored and not-censored for patient death). It is interesting to note that the rejection rate observed in either group was quite high (38% in the ESP group and 30% in the Control group), even though 43% of the patients in the ESP program received mono- or polyclonal induction and 47% triple-immunosuppressive therapy (Smits, et al., 2002). This result, especially in the ESP age-matching group, was somewhat surprising as it was generally accepted that immune responsiveness steadily decreases as the age of the recipient increases. Cox regression analysis to determine if the higher HLA mismatch might have been the explanation was not performed.

The same significant increase in the incidence of acute rejections (1 year: 43,2% for ESP vs. 27,4% for Control) was found in the local 3-year analysis of 69 ESP patients by Fritsche. However, this could be explained by the increased HLA mismatch in this group (Fritsche, et al., 2003). The Control group consisted of 71 renal transplant recipients aged 60 years or older who received organs from any age donor via ETKAS

Finally, a limited amount of results based on Eurotransplant data 3 years after starting the ESP were included in a recent publication by Cohen. Similar to the results after one year, the analysis of 876 transplants in the ESP demonstrated that 3-year graft survival rates censored for graft loss because of death were 70% compared with 71% in the control. No patient survival data are reported in this publication but the author concludes that the 3 year analysis shows no difference between patients who received grafts from elderly donors via ESP and those who received similar kidneys via the usual HLA-driven allocation procedure and suggests that, if care is taken to avoid the accumulation of additional risk factors such as long cold ischemic time and re-transplantation, an old-for-old allocation scheme can be operated successfully (Cohen, et al., 2005).

1.2   Rationale for performing this analysis

Preliminary evaluations of the program have shown that this program does not perceptibly harm the patients. However, as discussed above, available analyses of the program have limitations in terms of being single centre evaluations, a short follow-up, the use of different or historical controls as well as limited access to follow up data. Furthermore none of the existing analyses have performed any modelling/multivariate analyses looking for independent risk factors for long term outcomes. Information such as immunosuppressive regimens, biopsy proven rejection episodes, co-morbidities and hospitalizations are not part of the Eurotransplant database and thus have, if at all, only been part of the local evaluations.

All these factors combine to highlight the need to perform a more extensive ESP-5-year analysis on behalf of ETKAC. By collecting additional information on this unique cohort of prospectively age-matched elderly kidney transplant recipients over and above what is available in the Eurotransplant database and by looking at two different control groups, the results will serve as a base for further analyzing and improving the ESP allocation scheme. The number of ESP patients in this evaluation represents the biggest cohort of prospectively age-matched elderly renal transplant patients available for detailed analysis worldwide to date.

2   Objectives

2.1   Confirm primary ESP objectives

The primary objective of this 5 year evaluation was to determine if the allocation scheme met its goals of using kidneys from elderly donors more effectively and shortening the waiting time for elderly patients requiring kidney transplantation. The success of the program was evaluated by:

- The availability of elderly donors
- The waiting time for elderly recipients
- The cold ischemia time
- The main clinical outcomes of the renal transplantation such as patient and graft survival

2.2   Secondary objectives

Secondary objectives were:

- To assess renal function, acute rejection rates, and selected adverse events (infections, malignancies, CV events) compared to controls as well as published data in patients $\geq$ age 65
- To evaluate the impact of early graft function/degree of HLA match on long term outcomes, the impact of immunosuppressive regimes on outcomes, the duration of hospitalization and the frequency of readmission

3   Study Design

This is a retrospective study comparing the outcome of kidney transplant patients allocated in the Eurotransplant Senior Program (ESP) with the outcome of kidney transplant recipients of similar age allocated via the standard Eurotransplant kidney allocation system (ETKAS; Control).

Based on the definition of the ESP and the 2 Control groups (see 3.1 and 3.2), Eurotransplant provided data for a total of n=3456 patients transplanted between 4 January 1999 and 4 January 2004. For reasons detailed in 6.2, 25 patients were excluded from the analysis populations, giving a total of 3431 evaluable patients.

3.1   ESP- Group

Background information on the ESP can be found in section 1.1.5.

The study group (ESP group; old to old) consists of n=1406 patients. Patients in this group fulfil the criteria listed in the table below:

Table 3: ESP- eligibility criteria

recipient	age $\geq$ 65 years
	non-immunized at time of match (< 5% PRA)
	first transplant*
donor	age $\geq$ 65 years
allocation	local / regional
	disregard HLA matching
	based on waiting time and ABO compatibility only

*inclusion criteria were changed later on to also allow for second transplant

3.2 Control groups

There are two different Control groups based on either donor or recipient age. Donor organs in both Control groups were allocated via ETKAS that mandates exchange for zero-mismatched kidneys and allocates all other kidneys based on a combination of the number of HLA mismatches, chance of a good HLA match (mismatch probability), waiting time, expected cold ischemia time (distance between donor and recipient centre) and kidney exchange between participating countries (De Meester, et al., 1998).

Control group 1

Control group 1 consists of recipients of all age groups who received an organ from a donor aged 65 years or older via ETKAS. This Control group is relatively small (n= 446 pts) with most patients being transplanted in the first 2 years (1999-2001) before the ESP became part of the ETKAS. Control group 1 is of importance when analyzing parameters linked to the impact of donor age on outcomes.

Control group 1 (old to any) consists of n=446 patients

Control group 2

Control group 2 consists of recipients aged 60 to 64 years who received an organ from a donor of any age via ETKAS. The recipient age group of 60-64 years was selected for being the closest to the recipient age of the ESP patients. The size of this Control group is comparable to the size of the ESP group.

Control group 2 (any to old) consists of n=1687 patients
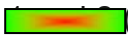
Table 4: Donor/recipient constellation and sample size of ESP and two Control groups

recipient / donor	> 65 ESP	>65 ETKAS	60-64 ETKAS	< 60 ETKAS
> 65 ESP				
>65 ETKAS				
60-64 ETKAS				
<60 ETKAS				

ESP Group (old to old) n = 1406

Control 1 (old to any) n= 446

Control 2 (any to old) n= 1687

Due to the definition of the two Control groups there is an overlap of 109 patients between Control   (   )

3.3 Participating Centres

All 64 renal transplant centres in the Eurotransplant region transplanted patients that fulfilled the criteria of at least one Control group were contacted and asked to provide missing and additional information. 50 centres representing >80% of patient data provided missing and additional data for the analysis.

For the first two years of the program (4 January 1999 to 4 January 2001) participation of the centres was on a strictly voluntary basis. As of 4 January 2001, the ESP became part of the ETKAS (Smits, et al., 2002). In the first year of the program N= 42 centres transplanted within the ESP, an additional 18 centres joined the program as of the second year. In total, N = 60 centres contributed ESP patients over the 5 year period 1999-2004.

3.4   Data capture

Eurotransplant maintains its own database (ENIS) that contains most of the information required for this analysis. However, only about 60% of the fields in ENIS had been completed and some additional parameters such as information on co-morbidities and hospitalizations, details of rejection episodes, immunosuppressive treatment and long term follow up were needed to allow for a more reliable and detailed analysis.

A user-friendly data collection tool based on an ACCESS 97 database was created and pre-populated with the existing data from the Eurotransplant database (ENIS), and new fields for the additional parameters were created. Centres were asked to complete the blank fields electronically. An introductory letter from Prof. Frei and Guido Persijn, the ETKAC secretary, was sent to all 64 ET centers on 2 November 2004 informing them about the project, introducing me as the responsible contact person and asking for their support. The database was closed on 15 May 2005. The completed database was transferred to (ENIS) and all copies of the database used for analysis within the working group were deleted (local copies remained).

4   Analysis Data Sets

The analysis of all primary and secondary endpoints is based on the set of all 3431 evaluable patients. For more details and exceptions concerning individual analyses see 6.2 and 6.4.

As a supportive analysis, selected endpoints, in particular those related to the primary objectives of the investigation, were evaluated for the following patient subset:

4.1   First ESP Year Set

While only 42 centres participated in the ESP in the first year, 60 centres transplanted ESP patients as of the second year. Given that in the first year, centres only gradually adjusted to the new program, the outcome for patients transplanted in the first year (4 January 1999 to 4 January 2000) was analyzed separately for comparison with both of the control groups as well as the complete 5 year analysis. In the results section that follows, only the results that are different from the main analysis or from the first year results published by Smits in 2002 (Smits, et al., 2002) are reported.

5 Study Endpoints

5.1 Endpoints related to primary objectives

- Number of transplanted organs from donors ≥65 years of age and proportion of the total donor pool by year of transplant
- Waiting time
- Cold ischemia time
- Clinical outcome
  Patient survival
  Graft survival
  Graft survival censored for patient death
  Death with functioning graft

5.2 Endpoints related to secondary objectives

5.2.1 Graft function

- Immediate graft function
- Delayed graft function
- Permanent non function
- Renal function as expressed by the serum creatinine at post-transplant week 2, month 3 and 6 and yearly thereafter
- Renal function assessed from calculated creatinine clearance at post-transplant week 2, month 3 and 6 and yearly thereafter

5.2.2 Acute rejection

- Proportion of patients experiencing any acute rejection during the first 6 and 12 months post-transplant
- Proportion of patients experiencing biopsy-proven acute rejection during the first 6 and 12 months post-transplant (separately for grade I and > I)
- Proportion of patients experiencing late acute rejection (> 1 year post-transplant)
- Number of rejection episodes per patient
- Time to first rejection (excluding cases with normal biopsy)

5.2.3 Adverse events

- Occurrence of a serious opportunistic infections at any time post transplant
- Occurrence of a malignancy at any time post transplant
- Occurrence of a cardiovascular event (defined as MI, bypass grafting, stroke or amputation) at any time post transplant

5.2.4 Hospitalization and the frequency of readmission

- In-hospital days for transplantation
- Number of readmissions to hospital/year of follow up
- Number of in-hospital days during readmissions to hospital/year of follow-up

5.2.5 Clinical condition

- Proportion of patients in poor clinical condition at time of most recent visit
- Proportion of patients in good clinical condition at time of most recent visit
- Proportion of patients in excellent clinical condition at time of most recent visit

6 Description of statistical methods and data presentation

6.1 General Considerations

The analysis of this study was conducted with an exploratory intent.

All analysis variables were tabulated with summary statistics, and graphical representations were used as appropriate. Statistical tests were used to highlight interesting aspects of the data, such as differences between the groups in the analyzed endpoints. The tests were conducted with a two-sided alternative and the p-values will be reported. Statistical significance is declared for p-values below 5%. If appropriate, 95% confidence intervals for point estimates based on suitable distributions were additionally provided. No correction of the significance level for multiple comparisons was performed.

In general the analysis variables were compared by means of statistical tests between the EPS group and the two Control groups taken separately.

All data analyses were performed using the statistical package R 2.0.1 (The R Foundation for Statistical Computing), for Windows XP. Statistical support was provided by Corrado Bernasconi, M.D. Ph.D.

6.2 Analysis population, completeness of data, patients per country

Based on the definition of the ESP and the 2 Control groups (see 2.1 and 2.2) Eurotransplant provided data on a total of 3456 patients transplanted between 4 January 1999 and 4 January 2004. 7 patients from non-heart beating donors and 18 ESP patients for whom either the donor or the recipient was less than 65 years of age at time of transplant were excluded from all analyses, leaving **a total number of 3431 patients for the analysis.** Due to the definition of the two Control groups there is an overlap of 109 patients between Control 1 and 2 (Table 5; see also 3.2.).

Table 5: Overview analysis populations

	N	%
Total number of patients (excluded patients: see below)	3431	100.00
ESP	1406	40.98
Control 1 (ETKAS, donor ≥ 65 y)	446	13.00
Control 2 (ETKAS, recipient ≥ 60 and	1687	49.17
Overlap between Control 1 and 2	109	3.18

Figure 7 shows the number of patients in each of the groups by year of transplantation. The number of patients transplanted in the ESP increased from 227 in 1999 to 382 in 2003.
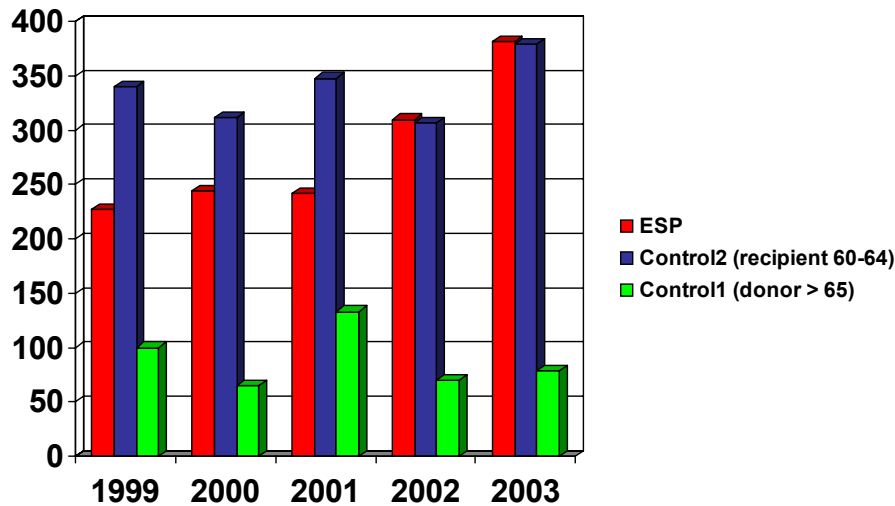
Figure 7: Number of patients transplanted by year

"Updated patient group": Out of 64 centres that were contacted and asked to provide missing information, 50 centres (79%) completed and returned data on a total of 2903 patients (85% of all patients, ESP Group n=1294; Control 1 n=355, and Control 2 n=1346 – considering also the overlaps)

The analysis for all evaluations concerning rejections was performed with the "updated patient population" only. In the data collection tool "no information" concerning rejection events and "no rejection" were not distinguished. Since detailed rejection data are available only for the "updated patient group", it was decided to restrict the analysis to this population.

The time of documented follow up was comparable in all groups indicating that there is no systematic error in the data capture (data not shown).

The majority of patients in all groups were transplanted in Germany (71.8%), followed by Austria (10.3%), Holland (9.1%) and Belgium (8%)(Figure 8). 83.8% of all ESP patients were transplanted in Germany.

Figure 8: Patients (all groups) per country

6.3 Missing data/outliers

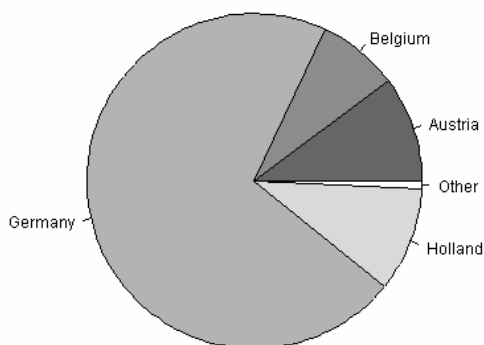No imputation of missing data was done. This implies that some of the analyses could in effect be performed only on a subset of the entire analysis population.

In particular for the analysis of patient and graft survival, several patients had to be excluded due to the fact that an event or censoring time could not be determined. Reasons were that such times were missing, negative (death, graft loss or loss to follow up reported as having occurred before transplantation) or events occurred after database closure (the maximum accepted event date was 06 June 2005). A maximum of 15.5% of the patients was excluded from such analyses.

As far as the analysis of rejection is concerned, it should be mentioned that the outcome "no rejection" could not be distinguished form the absence of rejection information. For analysis purposes, both cases were considered as no rejection, but the analysis population was restricted to the 2877 patients for which rejection information was collected.

With regard to SCr values it was agreed to exclude outliers (value < 10 or > 1000 μmol/l). Waiting times < 4 weeks and > 15 years were excluded from the waiting time analysis. However, values incorrectly expressed in mg/dl were kept if the value with supposedly correct unit fell between the 100-300 μmol/l limits.

6.4 Definition of main analysis and derived variables

6.4.1 Calculation of Creatinine Clearance

Creatinine Clearance was calculated using the Cockroft-Gault Formula (Cockcroft and Gault, 1976). Baseline demographic data for weight, height and gender at time of transplantation were used.

6.4.2 Acute rejection

Acute rejection episodes reported with a normal biopsy as well as cases with no biopsy and cases that were not treated were not considered acute rejections in the analysis.

6.4.3 Waiting time

The time on the waiting list for transplantation is defined as the time between first dialysis and transplantation.

6.4.4 Immunosuppressive therapy

When entering the immunosuppression at 6 and 12 Months the following time windows applied
- month 6   +/- 14 days
- month 12   +/- 1 months

6.4.5 Graft function

Immediate graft function: No dialysis required within the first 7 days post transplant

Delayed graft function: One or more dialysis required within the first 7 days post transplant.

When entering serum creatinine values the following time windows applied:
- week 2   +/- 2 days
- month 1   +/- 3 days
- month 3 und 6   +/- 14 days
- year 1-5   +/- 1 month

6.4.6 Adverse Events

"Yes" was recorded if an event occurred at any time during the observation period. The number of adverse events per patient was not recorded. Only selected adverse events were recorded: opportunistic infections, malignancies and cardiovascular events (see 5.2.3 for a definition)

6.4.7 Follow up on patient's last visit

Date last seen	Date of patient's most recent visit to the transplant centre and
Clinical condition	Clinical condition as judged by the treating physician (poor, good, excellent)

6.4.8 Hospital stay

Readmissions to hospital (number)	number of readmissions to hospital (= same location as transplant centre) for any reason during the observation period. Completion of this field seemed to cause some difficulties and inconsistencies might impact on analysis.
In hospital days during readmissions	cumulative number of days for all readmissions to hospital (= location as transplant centre) during the observation period. Completion of this field seems to cause some difficulties and inconsistencies might impact on analysis.

6.5   Demographic and Baseline Data

Demographic and background data are summarized for the ESP and the 2 Control groups.

The subdivision into categories of certain variables is only used in the presentation of summary statistics to but not in the statistical models except for the grouping of the reason for end-stage renal disease (ESRD), cause of graft loss and death, and the preservation solution.

6.6   Outline of statistical methods

Descriptive statistics were provided according to the nature of variables: number of observations, mean, standard deviation, minimum and maximum and quartiles for continuous variables, and frequency counts and percentages for categorical variables. Summary statistics were presented by group and in addition in selected cases broken down by other categorical variables, such as the transplantation year.

Continuous variables were compared by means of the Wilcoxon rank-sum test. Categorical variables, including proportions were analyzed with the chi-square test or in selected cases with Fisher's exact test. Survival times were analyzed using the Kaplan-Meier method. A plot of the estimated probabilities of survival was created and log-rank tests of the difference between groups in survival probabilities were carried out.

Cox regression analysis was used to additionally evaluate the impact of baseline and treatment characteristics (including HLA matches and selected IS regimens) on:

- Patient survival
- Graft survival
- Time to AR

Cox regression models were also used to evaluate early graft function and the occurrence of AR as predictors for patient and graft survival.

7 Results

7.1 Demographic and Baseline Data

7.1.1 Donor information

As expected, according to the definition of the groups the mean <u>donor age</u> was highest in the ESP group: 70.2 ± 4.3 years (range 65-93). Donor age in Control 1 (old to any) was comparable with the ESP group at 69.8 ± 4.2 years (range 65-87), while Control 2 (any to old) was lower at 45.1 ± 15.9 years (range 0,5-86). The distribution of the donor age is displayed in Table 6.

Table 6: Distribution of donor age

	age < 50	50 < = age < 65	65 < = age < 70	age > = 70
ESP	0 (0%)	0 (0%)	725 (51.6%)	680 (48.4%)
Control 1	0 (0%)	0 (0%)	255 (57.2%)	191 (42.8%)
Control 2	950 (56.3%)	628 (37.2%)	46 (2.7%)	63 (3.7%)

Interestingly, there were significantly <u>more female donors</u> in the ESP group (54.2%) compared to Control 2 (41.6%). <u>Donor serum creatinine</u> was comparable in all groups (mean ESP: 90.1± 50.1; Control 1: 93.8± 43.0; Control 2: 92.14±57.0). Given the considerably lower age in Control 2, this suggests an approximately 30% higher GFR for Control 2. Mean donor <u>body weight</u> was also comparable in all three groups (ESP: 76.6± 11.3; Control 1: 77.4± 12.0; Control 2: 75.29±16.24).   UW was the most commonly used <u>preservation solution</u> in all groups (62.2%) followed by HTK/Bretschneider (34.4%). In Control 2 UW was even more commonly used (66.9%) while HTK/Bretschneider was used slightly more often in the ESP group (38.9%).

The incidence of diabetes and hypertension recorded in the <u>medical history</u> of the donor was highest in the ESP group as indicated in the Table 7 below.

Table 7: Donor: diabetes and hypertension

	ESP	Control 1	Control 2
Diabetes mellitus	107 (16.9%)	20 (13.8%)	41 (6.2%)
Hypertension	776 (61%)	206 (55.2%)	410 (27%)

With 75.6% the most common <u>cause of death for donors</u> in all groups was natural death. In the Control group 2 (any to old) the percentage of traumatic cause of death was almost twice as high as in both the ESP and the Control 1 (Table 8).

Table 8: Donor: cause of death

	ESP	Control 1	Control 2	Total
a. traumatic	218 (15.5%)	74 (16.6%)	499 (29.6%)	775 (22.6%)
b. natural	1177 (83.7%)	368 (82.5%)	1141 (67.6%)	2594 (75.6%)
c. other	11 (0.8%)	4 (0.9%)	47 (2.8%)	62 (1.8%)

7.1.2 Recipient information

The mean <u>recipient age</u> at time of transplantation was highest in the ESP group at 67.7 ± 2.7 years (range 65-81). Mean age in Control 1 (old to any) was 57 ± 11.1 years (range 19-81) , and in Control 2 (any to old) was as expected according to the definition 63.6 ± 1.43 years (range 60-65). The distribution of the recipient age in defined categories is displayed in Table 9.

Table 9: Age of recipient at time of transplant in categories

	age < 50	50 < = age < 65	65 < = age < 70	age > = 70
ESP	0 (0%)	0 (0%)	1135 (80.7%)	271 (19.3%)
Control 1	108 (24.2%)	220 (49.3%)	93 (20.9%)	25 (5.6%)
Control 2	0 (0%)	1687 (100%)	0 (0%)	0 (0%)

Once again, there was a difference in gender distribution with significantly <u>more male recipients</u> in the ESP group (64,8%) compared to Control 2 (60%). Mean <u>body weight</u> of

the recipient was comparable in all three groups (ESP: 73,5± 13,5; Control 1: 73,1± 14,9; Control 2: 72,9±14,5)

The primary cause for ESRD is recorded in Table 10 with no apparent differences between the groups.

Table 10: End-stage renal disease of the recipient (categorized)

	ESP	Control 1	Control 2	Total
a. glomerular disease	366 (26.3%)	149 (34%)	447 (27.1%)	926 (27.4%)
b. interstitial disease (infectious/toxic)	203 (14.6%)	58 (13.2%)	214 (13%)	471 (14%)
c. polycystic / hereditary	203 (14.6%)	66 (15.1%)	341 (20.6%)	587 (17.4%)
d. vascular disease	117 (8.4%)	23 (5.3%)	116 (7%)	249 (7.4%)
e. diabetic nephropathy	131 (9.4%)	40 (9.1%)	147 (8.9%)	309 (9.2%)
f. systemic disease	22 (1.6%)	7 (1.6%)	27 (1.6%)	54 (1.6%)
g. unknown / others	349 (25.1%)	95 (21.7%)	360 (21.8%)	779 (23.1%)

The incidence of diabetes and hypertension reported in the medical history of the recipient was comparable in the three groups as shown in the table below. This information is not part of the Eurotransplant database and thus was only available for the datasets that have been updated.

Table 11: Pre-existing diabetes and cardiovascular disease in the recipient

	ESP	Control 1	Control 2	Total	NA
Diabetes mellitus	250 (23.8%)	46 (17.3%)	210 (20.4%)	492 (21.6%)	1155 (33.7%)
Cardiovascular disease	310 (29.6%)	73 (27%)	299 (28.9%)	657 (28.8%)	1149 (33.5%)

An analysis of the time on the waiting and of cold ischemia time list is presented in 7.2.2 and 7.2.3, as this pertains to the primary objectives of the study.

In order to reduce immunological risk, only non-immunized (panel-reactive antibody (PRA) <5%) recipients should be transplanted within the ESP. In our ESP analysis population 22 out of 1405 patients (1.6%) were highly sensitized, the remaining 98.4%

complied with the ESP rule. In both of the Control groups the number of highly sensitized patients was significantly higher at approximately 10% (p<0.001).

Table 12: PRA at transplantation >5%

	PRA < 5%	PRA > = 5%	Total	p-value
ESP	1383 (98.4%)	22 (1.6%)	1405 (100%)	-
Control 1	402 (90.5%)	42 (9.5%)	444 (100%)	< 0.0001
Control 2	1512 (89.9%)	170 (10.1%)	1682 (100%)	< 0.0001

7.1.3 Matching

In order to allow for local allocation of organs and to keep the cold ischemia times short the ESP allows ABO compatible transplantation disregarding human leukocyte antigen (HLA) matching. In contrast to this ETKAS allocates organs to identical blood group recipients only and tries to minimize HLA mismatch.

As a result, 86.4% of ESP patients compared with 94.4% of patients in Control 1 and 96.1% of patients in Control 2 had the identical blood group as their donor (p< 0.001 for both Controls versus ESP) and the mean (HLA)-mismatch was significantly higher in the ESP group than in both of the Controls (Table 13).

Table 13 Number of HLA-(A; -B, and –DR) mismatches

	n	min	Q1	med	mean	Q3	max	SD	p-value
ESP	1406	0.00	3.00	4.00	4.20	5.00	6.00	1.09	
Control 1	446	0.00	2.00	3.00	2.79	4.00	6.00	1.48	< 0.0001
Control 2	1687	0.00	1.00	2.00	2.04	3.00	6.00	1.44	< 0.0001

The distribution of the number of mismatches is illustrated in the figure below:
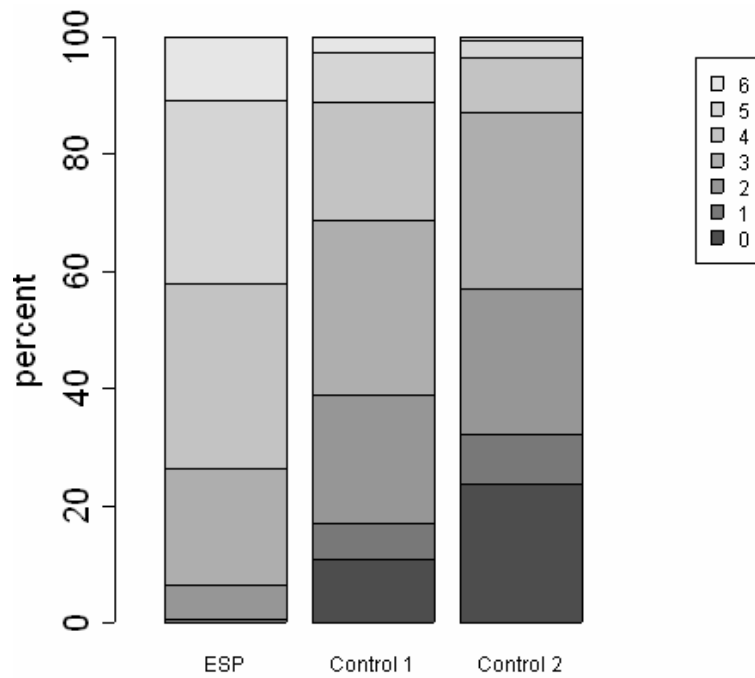
Figure 9: Distribution of number of mismatches

Consequently, the number of class I (HLA-A&B) and class II (HLA-DR) HLA-mismatches was significantly higher for the ESP group as well. 99.7% of ESP patients had at least 1 class I and 92.9% at least 1 class II mismatch. Details are given in Tables 14 and 15.

Table 14: Number of class I HLA mismatches (HLA-A&B)

	0	1	2	3	4	Total	p-value
ESP	4 (0.3%)	86 (6.2%)	365 (26.1%)	608 (43.5%)	335 (24%)	1398 (100%)	-
Control 1	57 (12.8%)	87 (19.5%)	156 (35%)	116 (26%)	30 (6.7%)	446 (100%)	< 0.0001
Control 2	443 (26.3%)	408 (24.2%)	560 (33.2%)	230 (13.6%)	46 (2.7%)	1687 (100%)	< 0.0001

Table 15: Number of class II HLA mismatches (HLA-DR)

	0	1	2	Total	p- value
ESP	99 (7.1%)	712 (50.9%)	587 (42%)	1398 (100%)	-
Control 1	128 (28.7%)	260 (58.3%)	58 (13%)	446 (100%)	< 0.0001
Control 2	762 (45.2%)	811 (48.1%)	114 (6.8%)	1687 (100%)	< 0.0001

7.1.4 Immunosuppressive regimen

Induction therapy with either polyclonal or monoclonal antibodies was more frequently administered in ESP Patients than in the two other groups. 20.8% of ESP patients received polyclonal induction therapy compared to 12.9% in Control1 and 12.2% in Control 2 (p< 0.001). Monoclonal induction therapy was reported in 34.9% of ESP patients and 29.6% of patients in Control 1 (p=ns) but only in 22.4% of Control2 (p< 0.0001).

Significantly more patients in the ESP group as compared to both Controls received MMF (ESP: 84.5%; Control 1: 78%, p=0,003; Control 2: 78.7%, p<0.0001). Significantly less patients in the ESP group as compared to both Controls received CsA (ESP: 63.1%; Control 1: 71.8%, p=0.002; Control 2: 76.2%, p<0.0001). 99.2% of all patients received corticosteroids with no significant differences between the groups. Triple therapy containing a calcineurin inhibitor was given to 81.1% of all patients as initial maintenance immunosuppression with no big differences in the groups and a similar decline at 6 and 12 months (57% still on triple therapy). Less than 10% of patients received a CNI free regimen initially or up to 12 month.

A summary of IS regimen administered in the three groups and changes in the first year is given below:

Table 16: Triple therapy (MMF/AZA + CsA/Tacro + Steroids): Summary

	ESP	Control 1	Control 2	Triple therapy	NA
Initial	1011 (79.9%)	317 (80.5%)	943 (82.4%)	2197 (81.1%)	723 (21.1%)
Month 6	587 (69.2%)	171 (75.7%)	636 (66.6%)	1349 (68.5%)	1462 (42.6%)
Month 12	471 (59.1%)	132 (61.4%)	493 (54.1%)	1066 (57%)	1562 (45.5%)

Table 17: CNI-free therapy (no CsA and no Tacro): Summary

	ESP	Control 1	Control 2	CNI-free	NA
Initial	169 (13.3%)	27 (6.8%)	44 (3.7%)	236 (8.6%)	683 (19.9%)
Month 6	82 (9.4%)	13 (5.6%)	49 (5%)	140 (6.9%)	1413 (41.2%)
Month 12	84 (10.3%)	16 (7.1%)	82 (8.7%)	178 (9.3%)	1507 (43.9%)

7.2   Endpoints related to primary objectives

7.2.1   Increased availability of elderly donors

Prior to ESP, 10% of all used donor kidneys were retrieved from donors over 65 years of age. Since the implementation of the ESP in 1999, this proportion has increased to 14.5% (Figure 10 and Table 18).

Figure 10 and Table 18: The number of post mortem donors used for renal transplantation,   stratified for donor's age

7.2.2   Waiting time

The median time on the waitlist (time between first dialysis and transplantation) for the ESP group versus Control 1 (old to any) was comparable (3.6 years and 3.8 years, respectively) but significantly shorter than for Control 2 (any to old; 4.6 years; p<0.0001)

	n	min	Q1	med	mean	Q3	max	SD	NA	p-value
ESP	1406	0.16	2.34	3.55	3.89	5.36	13.05	2.01	88	
Control 1	446	0.25	2.34	3.79	4.21	5.90	14.99	2.47	68	0.126
Control 2	1687	0.12	2.71	4.64	4.93	6.96	13.80	2.65	256	<0.0001

Table 19: Waiting time on the transplantation list

In the first year analysis set all three groups had a comparable median time on the waitlist of 3.94 years for ESP; 3.61 for Control 1 (old to any) and 3.89 for Control 2 (any to old).

7.2.3 Cold ischemia time

97% of the organs in the ESP program were, as expected, allocated locally or regionally, as compared to only half of the organs transplanted via ETKAS.

Table 20: Allocation mode of donor organs

	Abroad	Home country	Local/Regional
ESP	2 (0.1%)	44 (3.1%)	1360 (96.7%)
Control 1	84 (18.9%)	143 (32.1%)	218 (49%)
Control 2	335 (19.9%)	492 (29.2%)	860 (51%)

The cold ischemia time in the ESP group was significantly shorter with a mean of 11.9 ±5.2 hours compared with over 17 hours in both Control groups (Control 1: 17.8 ± 6.8; Control 2: 17.5 ± 6.4; p<0.001) (Figure 11). 26% of organs transplanted in the ESP had cold ischemic times below 8 hours (Table 21).

Looking at the first year analysis set, cold ischemia times for ESP patients still were significantly shorter compared to both of the controls, but generally all three groups had longer cold ischemia times (ESP: 13.01 ± 5.7; Control 1: 19.4 ± 6.9; Control 2: 18.8 ± 6.4).

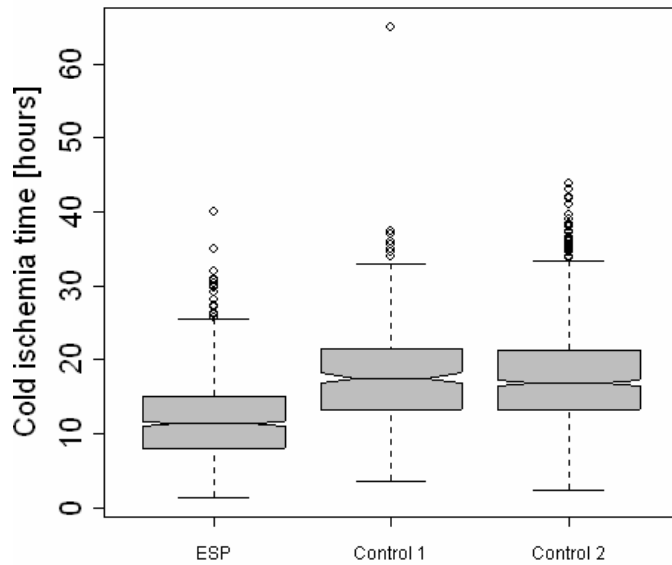Figure 11: Cold ischemia time

Table 21: Cold ischemia time below 8 hours, 8-12 and more than 12 hours

	0-8 h	8-12 h	> 12 h	Total	NA	p-value
ESP	350 (25.7%)	426 (31.2%)	588 (43.1%)	1364 (100%)	42 (3%)	-
Control 1	26 (6.2%)	53 (12.7%)	338 (81.1%)	417 (100%)	29 (6.5%)	<0.0001
Control 2	81 (5%)	223 (13.8%)	1316 (81.2%)	1620 (100%)	67 (4%)	<0.0001
Tot. patients	452 (13.7%)	690 (20.9%)	2156 (65.4%)	3298 (100%)	133 (3.9%)	

7.2.4 Outcome

Actual <u>patient survival</u> according to Kaplan-Meier is shown in Figure 12. The ESP (old to old) group had the lowest 5 year patient survival rates with 60% compared to 71% and 74% for Control 1(old to any) and 2 (any to old) respectively. The log rank test for differences between the groups was significant for both comparison EPS vs. Control 1 (p = 0.0488) as well as for EPS vs. Control 2 (p < 0.0001).
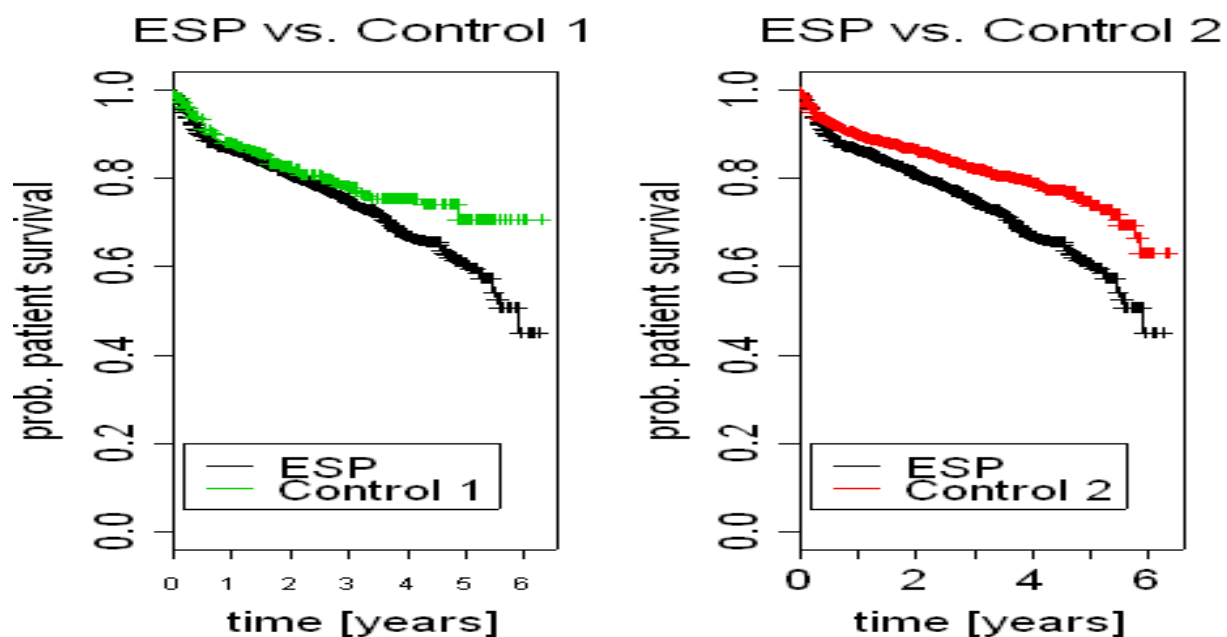
Figure 12 : Kaplan-Meier Analysis of patient survival for ESP patients (old to old) versus Control 1 (old to any) and Control 2 (any to old)

An important remark regarding Control 1 is that the survival curve is very flat from the third year on, when it clearly diverges from the ESP curve. In particular, no deaths are reported after 4.85 years post transplantation. Chance (no deaths in a small population at risk) and/or underreporting of late death cases are probably the largest contributors to the described flattening

When patients in Control 2 were analyzed separately for donor age < 60 (Control 2 d< 60, n=1100) and ≥ 60 years of age (Control 2 d ≥ 60, n=275), the Kaplan-Meier survival shows a clear spilt of the two subpopulations, and no statistically significant differences between ESP and Control 2 d ≥ 60 were found. 5-year patient survival for the ESP group of 60% now compared to 67% for Control 2 d ≥ 60 and 76% for Control 2 d < 60 (Figure 13).
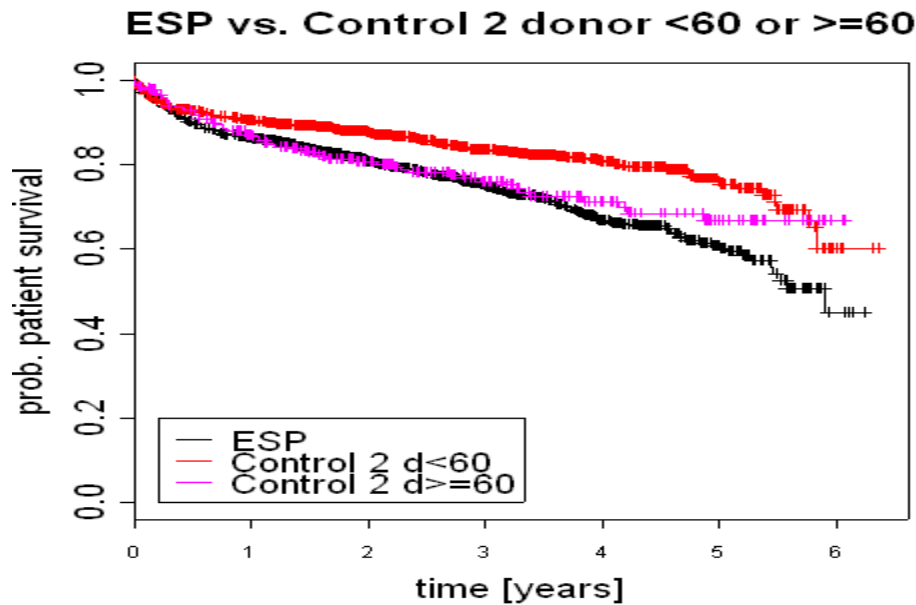
Figure 13 Kaplan-Meier Analysis of patient survival for ESP patients (old to old) versus Control 2 stratified by donor age < and ≥ 60 years.

After 5 years, <u>patient and graft survival (= uncensored graft survival)</u> was 47% for the ESP group compared to 51 and 64%, respectively, for Control 1 and Control 2. Figure 14 shows the probability of graft survival for the ESP (old to old) group compared to Control 1 (old to any) and Control 2 (any to old). The log rank test for differences between the groups was not significant for the comparison EPS vs. Control 1 (p = 0.6248) but highly significant for the comparison EPS vs. Control 2 (p < 0.0001).
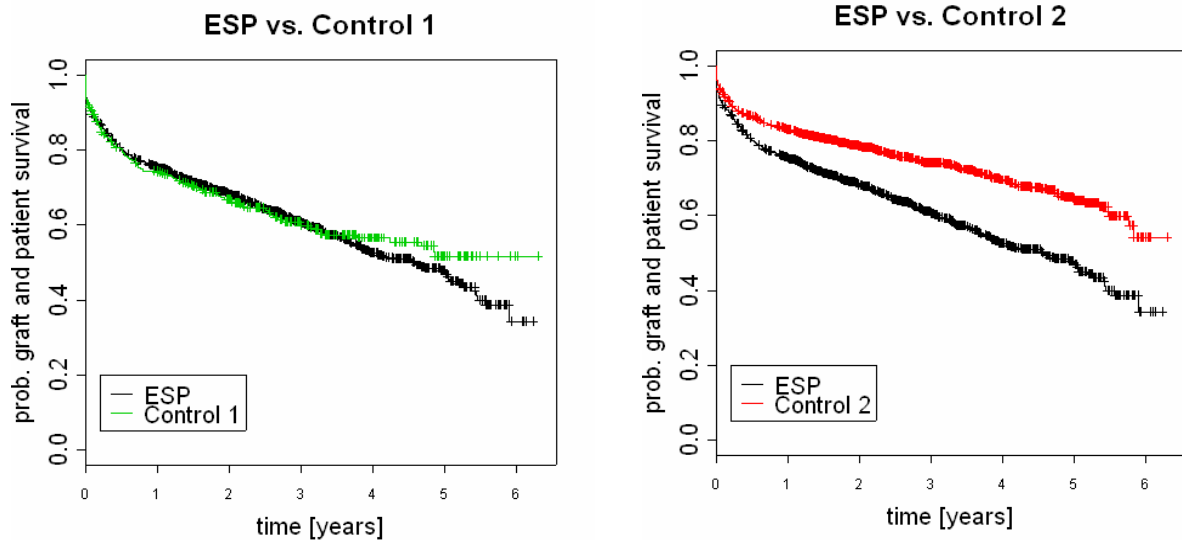
Figure 14: Kaplan-Meier Analysis of patient and graft survival for ESP patients (old to old) versus Control 1 (old to any) and Control 2 (any to old)

The Kaplan Meier curve for the sub analysis of patients in Control 2 with donor age < 60 (Control 2 d< 60) and ≥ 60 years of age (Control 2 d ≥ 60) revealed the same spilt for the uncensored graft survival as for the patient survival. 1 and 5-year patient and graft survival for the ESP group of 75 and 47% now compared to 74 and 53% for Control 2 d ≥ 60 (p= 0,38) and 85 and 67% for Control 2 d < 60 (Figure 15).
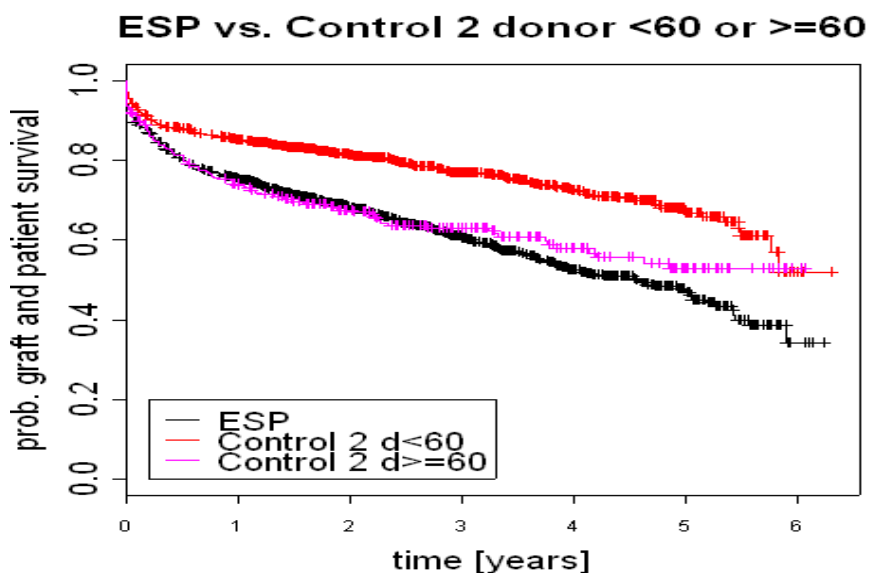

Figure 15 Kaplan-Meier Analysis of patient and graft survival for ESP patients (old to old) versus Control 2 stratified by donor age < and ≥ 60 years.

Figure 16 depicts the probability of graft survival when losses of graft as a result of the patient death were censored. Graft survival rates censored for death with function at 5 years were 67% for ESP (old to old) and Control 1 (old to any) compared to 81% for Control 2 (any to old). The log rank test showed no significant differences for the comparison EPS vs. Control 1 (p = 0.5519) but highly significant for the comparison EPS vs. Control 2 (p < 0.0001).
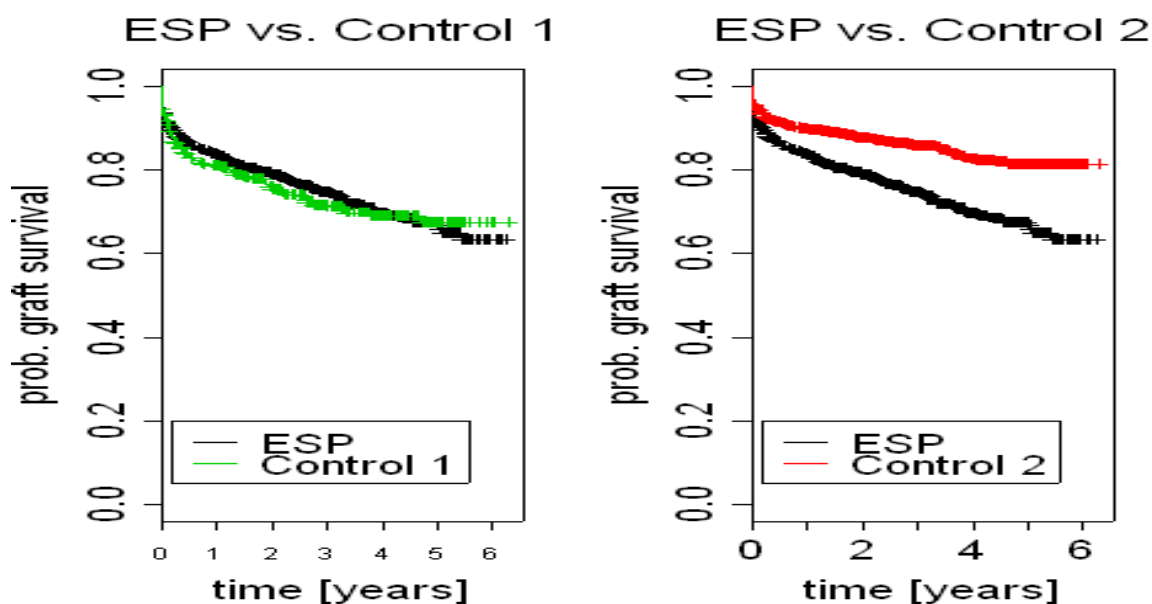

Figure 16: Kaplan-Meier Analysis death censored graft survival for ESP patients (old to old) versus Control 1 (old to any) and Control 2 (any to old)

Overall, death with functioning graft occurred in 76,6% of patients with no significant differences between the three groups (ESP: 75.3%; Control 1: 74.6%; Control 2: 77.4%; p=ns). The most common reason for graft loss in all groups was rejection (overall 30.9%). Patients in Control 1 lost more grafts due to rejection (42.4%) as compared to ESP (29.5) or Control 2 (28.8%), but the numbers are relatively small. Details can be found in the table below:

Table 22: Reason for graft loss

	ESP	Control 1	Control 2	Total
a. rejection	94 (29.5%)	42 (42.4%)	64 (28.8%)	188 (30.9%)
b. recurrent disease	3 (0.9%)	0 (0%)	3 (1.4%)	6 (1%)
c. technical / vascular	42 (13.2%)	9 (9.1%)	27 (12.2%)	75 (12.3%)

d. infection	37 (11.6%)	7 (7.1%)	22 (9.9%)	62 (10.2%)
e. non-function (primary)	47 (14.7%)	19 (19.2%)	33 (14.9%)	94 (15.5%)
f. other /unknown	96 (30.1%)	22 (22.2%)	73 (32.9%)	183 (30.1%)
Total	319 (100%)	99 (100%)	222 (100%)	608 (100%)

Almost 60% of all patients that died, did so due to infectious or cardiovascular event. Interestingly, death due to cardiovascular events occurred slightly less often in the ESP group (22.9%) compared with Control 1 (32.4%) and 2 (32.5%)(Table 23).

Table 23: Cause of death

	ESP	Control 1	Control 2	Total
a. cardiovascular	67 (22.9%)	23 (32.4%)	75 (32.5%)	156 (27.2%)
b. infectious	90 (30.7%)	21 (29.6%)	69 (29.9%)	174 (30.3%)
c. malignant	27 (9.2%)	3 (4.2%)	19 (8.2%)	49 (8.5%)
d. others (defined)	50 (17.1%)	13 (18.3%)	38 (16.5%)	97 (16.9%)
e. unknown / not determined	59 (20.1%)	11 (15.5%)	30 (13%)	98 (17.1%)
Total	293 (100%)	71 (100%)	231 (100%)	574 (100%)

7.3   Endpoints related to Secondary Objective

7.3.1 Graft function

A direct primary functioning kidney graft was obtained for 63% of ESP patients compared with 55.5% of Control 1 (p= 0.009) and 63.8% of Control 2 patients (p=ns). Delayed graft function was seen in 29.7%; 36.2% and 30.9% of the ESP, Control 1 and Control 2 transplants, respectively (ESP vs. Control 1 p= 0.047; ESP vs. Control 2 p= ns), and kidneys suffered permanent non-functioning in 7.3%, 8.3.% and 5.0% of patients in each group, respectively (Figure 17) .
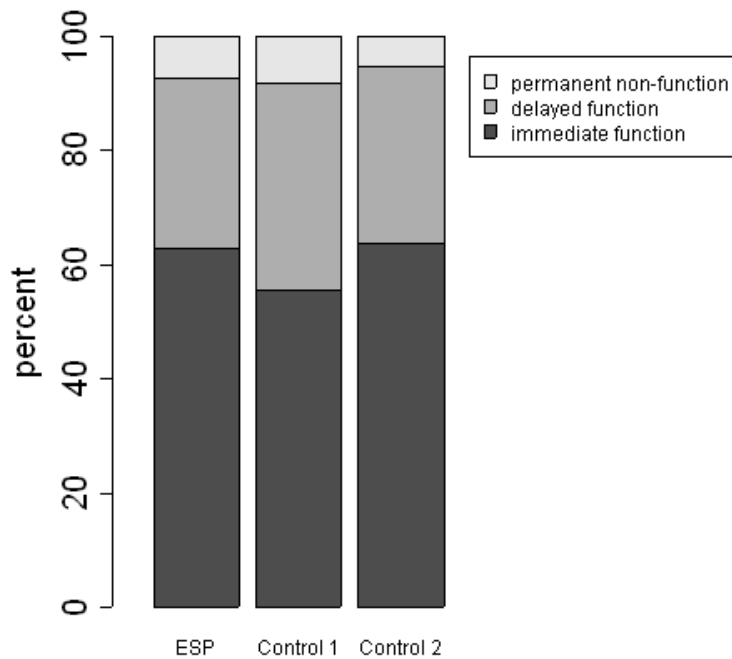
Figure 17: Post-transplant graft function- Overview

Renal function as expressed by the serum creatinine at post-transplant week 2 was highest with a median SCr of 153 µmol/l (range 53-910) in Control 2 (any to old). The median SCr value in the ESP group of 186 µmol/l (range 53-970) was significantly higher (p < 0,0001) but still significantly lower than Control 1 (median SCr 210 µmol/l; range 64-919; p = 0,007). At six months, a median SCr of 127 µmol/l in Control 2 compared to 159 µmol/l in the ESP and 167 µmol/l in Control 1. Similar differences in graft function were maintained over time with ESP patients having higher SCr values and lower calculated GFRs compared to Control 2 (any to old) but lower SCr values and comparable calculated GFRs compared to Control 1 (old to any).(Figures 18 a and b).
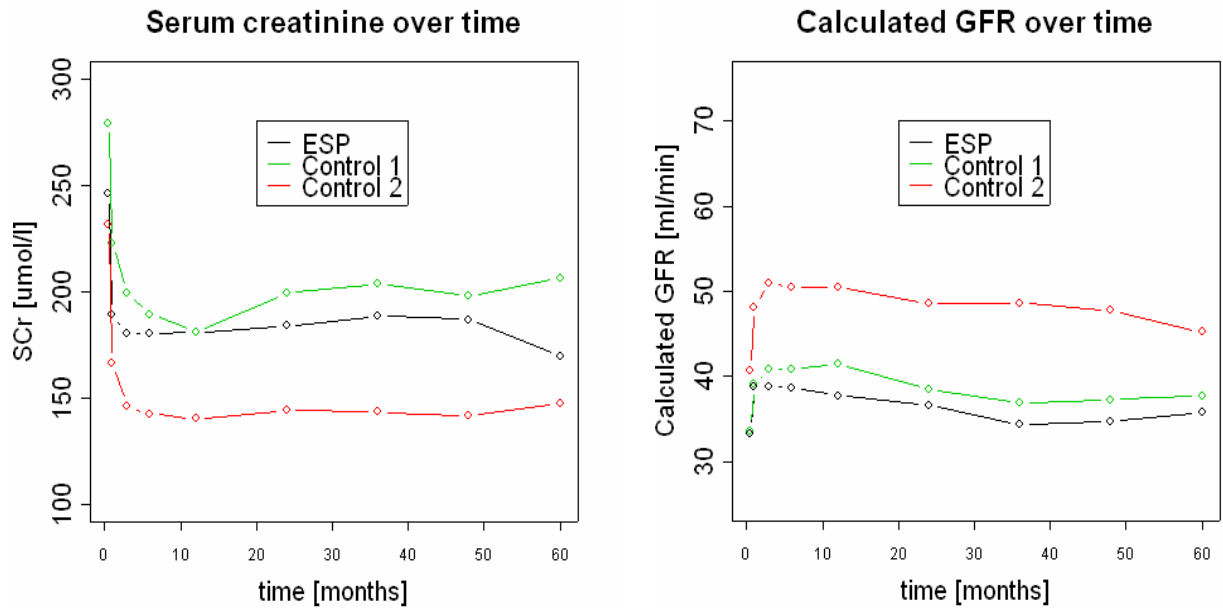
Figure 18 a/b: Renal function in the three groups assessed at post-transplant week 2, month 3 and 6 and yearly thereafter **a)** SCr values **b)** Calculated Creatinine Clearance using the Cockroft-Gault Formula.

7.3.2 Acute rejection

The proportion of patients experiencing at least one rejection episode at any time post transplant in the ESP group (29.1%) was comparable with Control 1 (24.3%; p = 0.087) but significantly higher than in Control 2 (20.1%; p < 0.0001). Overall, out of all patients with at least one rejection episode, 78.7% experienced one episode, 15.9% had two episodes and only 5.5% had three episodes of rejection with no significant differences between groups. The number of biopsy proven acute rejection episodes was 19.4% in the ESP group. This is comparable to Control 1 (15.9 %; p = 0.16) but significantly higher than in Control 2 (12.4%; p < 0.0001). Most rejections in all groups occurred in the first 6 months. Less than 2% occurred between months 6 and 12 post-transplant and less than 3% late acute rejections beyond the first year were recorded.

Kaplan-Meier analysis for rejection is shown in Figure 19. The log rank test for differences between the groups was significant for both comparison EPS vs. Control 1 (p = 0.0431) as well as for EPS vs. Control 2 (p < 0.0001).
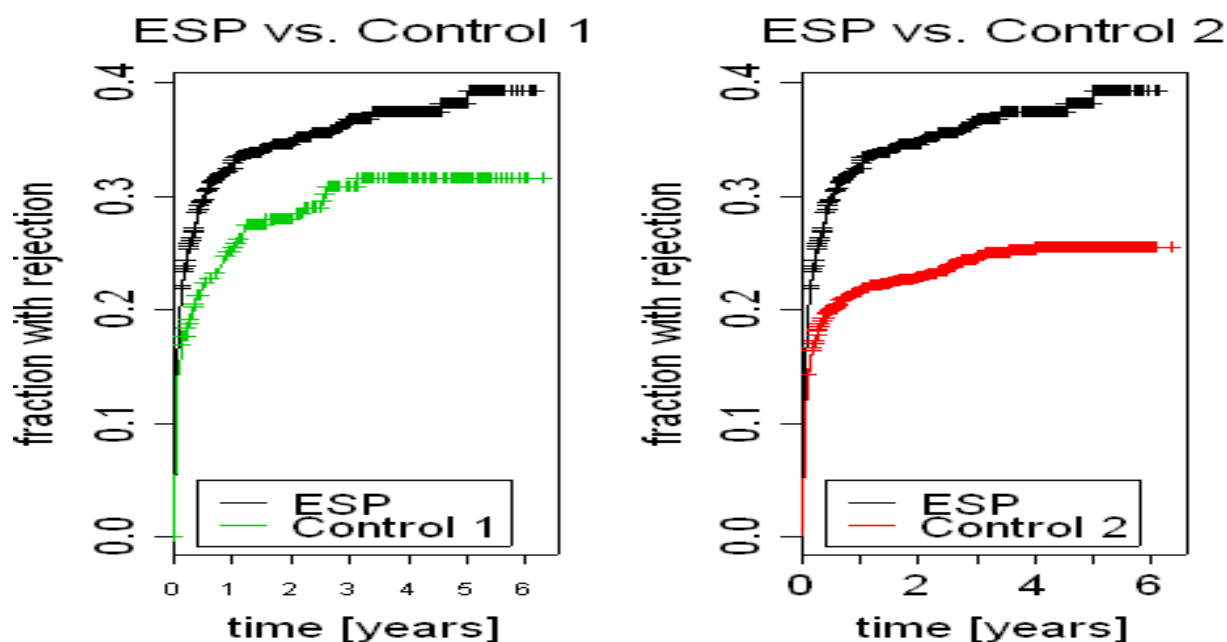
Figure 19: Kaplan-Meier estimates for rejection

7.3.3 Adverse events

This information is not captured in the ET database and was added to the data collection toll. Thus, information is limited to the completed patient population and percentages are calculated accordingly.

Occurrence of serious opportunistic infections at any time post transplant was very common and highest in ESP (51%) and Control 1 (50.4%) patients compared to 38.8% in Control 2. Overall, cardiovascular events (defined as MI, bypass grafting, stroke or amputation) and malignancies at any time post transplant were reported in 14.3% and 9.5% of all patients, again with the highest incidence in the ESP group (15.2% and 10.3 % respectively) (Table 24)

Table 24: Incidence of serious adverse events at any time after transplant

	ESP	Control 1	Control 2	Total	NA
Infection	491 (51%)	125 (50.4%)	377 (39.8%)	959 (45.8%)	1335 (38.9%)
Cardiovascular event	147 (15.2%)	29 (11.7%)	132 (14%)	299 (14.3%)	1339 (39%)
Malignancy	100 (10.3%)	18 (7.3%)	85 (9%)	199 (9.5%)	1333 (38.9%)

7.3.4 Hospitalization and the frequency of readmission

The median number of in-hospital days for transplantation was 27 days for ESP (range 2-109) and Control 1 (range 7-136) compared to 25 days (range 1-170) for patients in Control 2 (ESP vs. Control 2: p<0.0001). ESP patient were reported to be significantly more often readmitted to hospital per year of follow up compared to both of the Controls (median number of hospital stays per year of follow up ESP: 1.01 (range 0-59); Control 1: 0.78 (range 0-28); Control 2: 0.71 (range 0-21)). The number of in-hospital days during readmissions to hospital per year of follow-up was also longest for the ESP group (Table 25)

Table 25: Days in hospital per year in follow-up [days/year]

	n	min	Q1	med	mean	Q3	max	SD	NA	p-value
ESP	1406	0.00	4.53	11.09	29.12	30.95	559.15	51.80	641	
Control 1	446	0.00	3.68	9.84	25.50	25.62	397.21	47.95	232	0.241
Control 2	1687	0.00	2.16	7.00	20.65	17.69	2206.40	87.64	927	<0.0001

7.3.5 Clinical condition

The clinical condition at the most recent visit was judged by the attending physician as poor for 20.1% of ESP patients compared to 12.9% of patients in Control 1 and 10.1% of patients in Control 2. Table 26 depicts an overview of the patient status in the three groups.

Table 26: Clinical condition of the patient at most recent visit as judged by attending physician

	excellent	good	poor	Total	NA	p-value
ESP	59 (6.8%)	636 (73.1%)	175 (20.1%)	870 (100%)	536 (38.1%)	-
Control 1	24 (10.3%)	178 (76.7%)	30 (12.9%)	232 (100%)	214 (48%)	0.014
Control 2	150 (15.7%)	711 (74.2%)	97 (10.1%)	958 (100%)	729 (43.2%)	<0.0001
Total	226 (11.3%)	1477 (74%)	293 (14.7%)	1996 (100%)	1435 (41.8%)	

7.4 Regression Models

Cox regression analysis was used to additionally evaluate the impact of baseline and treatment characteristics on patient and graft survival.

Each of the following tables summarizes the result of the multiple Cox regression models after Akaike's Information Criterion (AIC)-based backwards selection. AIC is used to compare several (nested) models.

7.4.1 Cox regression: patient survival in ESP and Control 1

The Cox regression analysis for patient survival in ESP and Control 1 revealed that significant independent risk factors of patient survival were ESP group, recipient gender, delayed graft function, donor age, graft loss and recipient diabetes and a preservation solution other than UW. Patients experiencing graft loss had a > 200% increased risk of death (RR= 3.07; p< 0.0001); patients with diabetes were 1.7 times more likely to die (RR= 1.77; p< 0.0001), and DGF increased the risk of death by 40% (RR= 1,41; p= 0.011). For each year of donor age the risk of death increases by 3.5%, male recipients have 50% higher relative risk and use of a preservation solution other than UW almost doubled the risk. The other factors listed in Table 27 are relevant as well but were not statistically significant.

Table 27: Multiple Cox regression model after AIC-based backward selection for patient survival in ESP and Control 1 (n=1148)

Risk Factor	Category	Relative Risk	lower 0.95 CL	upper 0.95 CL	p-value
ESP group	**True**	**1.86233**	**1.26343**	**2.74513**	**0.0017**
Recipient gender	**Male**	**1.47955**	**1.08522**	**2.01715**	**0.013**
Donor SCr	10 µmol/l	1.00155	0.9982	1.00491	0.37
Waiting time	Year	1.00303	0.97735	1.02939	0.82
Cold ischemia time	Hour	0.98463	0.95985	1.01004	0.23
Delayed graft function	**Yes**	**1.41244**	**1.08405**	**1.84032**	**0.011**
Recipient weight	kg	0.98758	0.97574	0.99958	0.042
Donor age	**Year**	**1.03465**	**1.00584**	**1.06428**	**0.018**
HLA mismatch Class II	Per mismatch	0.91792	0.74733	1.12746	0.41
Graft loss	**True**	**3.06996**	**2.30503**	**4.08874**	**< 0,0001**
Recipient Diabetes	**True**	**1.77581**	**1.34293**	**2.34823**	**< 0,0001**
Preservation solution	**Other**	**1.9415**	**1.0973**	**3.43516**	**0.023**
Preservation solution	UW	1.09727	0.83917	1.43476	0.5

7.4.2 Cox regression: patient survival in ESP and Control 2

In the same model for ESP and Control 2 recipient gender was not associated with an increased risk but the model showed one new independent risk factor compared to the ones described in 7.4.1. In this model patient survival was significantly influenced by reported cardiovascular disease. Cardiovascular disease in the medical history of the recipient increased the risk of death by almost 40% (RR= 1.39; p= 0.0067). Again, graft loss and preservation solution other than UW appeared to be strongly associated with an increased risk of death.

Table 28: Multiple Cox regression model after AIC-based backward selection for patient survival in ESP and Control 2 (n=1756)

Risk factor	Category	Relative Risk	lower 0.95 CL	upper 0.95 CL	p-value
ESP Group	**True**	**1.79549**	**1.31829**	**2.44544**	**< 0,0001**
Recipient gender	Male	1.26476	0.96981	1.64941	0.083
Donor SCr	10 µmol/l	1.00005	0.99999	1.00012	0.087
Waiting time	Year	0.99883	0.99677	1.0009	0.27
HLA mismatch Class I	Per mismatch	1.00799	0.89768	1.13185	0.89
Cold ischemia time	Hour	0.98989	0.96992	1.01026	0.33
Rejection	Yes	0.81561	0.63695	1.04439	0.11
Delayed graft function	**Yes**	**1.38633**	**1.10238**	**1.74341**	**0.0052**
Recipient Diabetes	**True**	**1.37636**	**1.07104**	**1.76872**	**0.013**
Recipient CV disease	**True**	**1.39205**	**1.0958**	**1.76841**	**0.0067**
Graft Loss	**True**	**3.54001**	**2.7474**	**4.56129**	**< 0,0001**
Preservation solution	**Other**	**1.92702**	**1.13083**	**3.28381**	**0.016**
Preservation solution	UW	1.15667	0.90997	1.47025	0.23
Recipient weight	kg	0.99975	0.99019	1.0094	0.96

Since the ESP group and the Control 2 differ significantly in both donor as well as recipient age, a model for age of donor and recipient as the only factors was created for Control 2. The model was then used to predict survival in putative patients transplanted according to the protocol used for Control 2 but with a donor and recipient age comparable to the ESP group.

In the model, both donor and recipient age were highly significantly associated with patient survival (p<0.001 for both factors). The relative risk of death was about 2% and 1% for each additional year of age of the recipient and the donor, respectively. No relevant interaction between the two factors appeared to be present. Figure 20 shows the probability of patient survival for Control 2 compared to the extrapolated Control 2. The higher mean donor and recipient age in the extrapolated curve explains the large survival difference.

A comparison of survival in ESP and the extrapolated Control 2 over the first 5 years post-transplantation points to a slight but systematic survival advantage for patients transplanted under the ESP (Table 29)
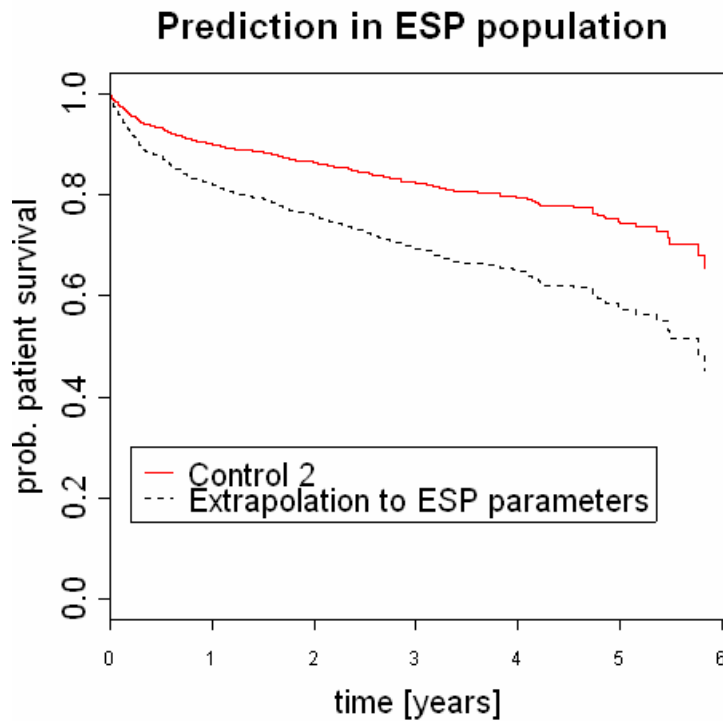

Figure 20: Kaplan-Meier Analysis of patient survival for Control2 versus Control 2 extrapolated to ESP parameters

Table 29: Comparison of survival in ESP group with extrapolation from Control 2

	Year 1	Year 2	Year 3	Year 4	Year 5
ESP Group	0.86	0.81	0.75	0.67	0.60
Control 2 (extrapolated to ESP parameters)	0.82	0.76	0.69	0.65	0.58

7.4.3 Cox regression: patient & graft survival in ESP and Control 1

Patient and graft survival (uncensored graft survival) was significantly influenced by male gender of recipient (RR= 1.441; p=0.0021), delayed graft function (RR= 1.32; p= 0.0091); donor age (RR= 1.043; p = 0.0017) and diabetes of the recipient. The latter one increased the risk by 27% (RR= 1.268; p = 0.0044).

Table 30: Multiple Cox regression model after AIC-based backward selection for patient and graft survival (uncensored graft survival) in ESP and Control 1

Risk factor	Category	Relative Risk	lower 0.95 CL	upper 0.95 CL	p-value
ESP Group	True	1.24841	0.93324	1.67003	0.14
Recipient gender	**Male**	**1.46728**	**1.15786**	**1.85938**	**0.0015**
Donor SCr	10 µmol/l	1.00146	0.99868	1.00425	0.3
Waiting time	Year	1.00332	0.98162	1.02549	0.77
HLA mismatch Class I	Per mismatch	1.05997	0.95308	1.17886	0.28
Cold ischemia time	Hour	1.00065	0.98129	1.02039	0.95
Delayed graft function	**Yes**	**1.31904**	**1.07132**	**1.62405**	**0.0091**
Recipient weight	Kg	0.99358	0.98483	1.00241	0.15
Donor age	**Year**	**1.0426**	**1.02021**	**1.06549**	**0.00017**
Preservation solution	Other	1.41375	0.86087	2.3217	0.17
Preservation solution	UW	0.95598	0.77761	1.17525	0.67
Recipient diabetes	**True**	**1.26891**	**1.00677**	**1.59932**	**0.044**

7.4.4 Cox regression: patient & graft survival in ESP and Control 2

The model for patient & graft survival in ESP and Control 2 only identified three significant risk factors: The ESP group itself, male gender of the recipient and delayed graft function. Details of the increase in risk can be found in Table 30.

Table 31 Multiple Cox regression model after AIC-based backward selection for patient and graft survival (uncensored graft survival) in ESP and Control 2

Risk factor	Category	Relative Risk	lower 0.95 CL	upper 0.95 CL	p-value
ESP Group	**True**	**1.57011**	**1.20818**	**2.04046**	**0.00074**
Recipient gender	**Male**	**1.47239**	**1.19345**	**1.81653**	**0.00031**
Donor SCr	10 µmol/l	1.00016	0.99955	1.00077	0.61
Waiting time	Year	0.99835	0.99627	1.00042	0.12
HLA mismatch Class I	Per mismatch	1.08261	0.98617	1.18848	0.095
Cold ischemia time	Hour	1.002	0.9857	1.01856	0.81
Delayed graft function	**Yes**	**1.3979**	**1.16293**	**1.68033**	**0.00036**
Recipient weight	Kg	0.99906	0.99153	1.00665	0.81
Preservation solution	Other	1.20359	0.74619	1.94137	0.45
Preservation solution	UW	0.97696	0.80872	1.1802	0.81

7.4.5 Cox regression: graft survival (censored for death with functioning graft) in ESP and Control 1

Male recipients, cold ischemia time and donor age were the only three independent predictors of death censored graft survival in the model for ESP and Control 1. Male recipients had a 74% increased risk of graft loss (RR= 1.742; p < 0.0001). For every hour of cold ischemia time the risk of graft loss increased by 3% and for each year of donor age the risk of graft loss increased by 6% (RR= 1.058; p<0.0001).

Table 32: Multiple Cox regression model after AIC-based backward selection for graft survival (censored for DwFG) in ESP and Control 1 (n=1125)

Risk factor	Category	Relative Risk	lower 0.95 CL	upper 0.95 CL	p-value
Recipient gender	**Male**	**1.74251**	**1.26405**	**2.40209**	**< 0.0001**
Donor SCr	10 µmol/l	1.00048	0.99656	1.00441	0.81
Waiting time	Year	1.00314	0.9653	1.04245	0.87
HLA mismatch Class I	Per mismatch	1.111	0.96797	1.27516	0.13
HLA mismatch Class II	Per mismatch	1.26872	1.02095	1.57661	0.032
Cold ischemia time	**Hour**	**1.02769**	**1.00301**	**1.05298**	**0.028**
Delayed graft function	Yes	1.22412	0.92653	1.61729	0.15
Recipient weight	kg	0.9971	0.98585	1.00847	0.62
Recipient CV disease	True	0.74947	0.53699	1.04604	0.09
Donor age	**year**	**1.05888**	**1.02944**	**1.08916**	**< 0.0001**
Preservation solution	Other	1.00475	0.46188	2.18569	0.99
Preservation solution	UW	0.90563	0.68839	1.19143	0.48

7.4.6 Cox regression: graft survival (censored for DwFG) in ESP and Control 2

Death censored graft survival in ESP and Control 2 was influenced by a number of variables including ESP group, male gender, HLA class I mismatch and delayed graft function. Interestingly, male recipient was determined as the strongest risk factor in this analysis increasing the risk of graft loss by 66% (RR= 1.659; p = 0.00066). For every mismatch in class I the risk for losing the graft increased by 15%(Table 33).

7.4.7 Cox regression: rejections in ESP and Control 1

A HLA class II mismatch conferred a 1.217 relative risk of graft rejection, and delayed graft function increased the risk of rejection by over 50% (RR= 1.524; p< 0.0001) when analyzed in the Cox regression model (Table 34).

Table 33: Multiple Cox regression model after AIC-based backward selection for graft survival (censored for DwFG) in ESP and Control 2 (n=1715)

Risk factor	Category	Relative Risk	lower 0.95 CL	upper 0.95 CL	p-value
ESP Group	**True**	**1.47312**	**1.03028**	**2.10629**	**0.034**
Recipient gender	**Male**	**1.65926**	**1.23966**	**2.22089**	**0.00066**
Donor SCr	10 µmol/l	0.9992	0.9964	1.00201	0.58
Waiting time	Year	0.9978	0.99576	0.99985	0.036
HLA mismatch Class I	**Per mismatch**	**1.14974**	**1.01113**	**1.30736**	**0.033**
HLA mismatch Class II	Per mismatch	1.18215	0.96455	1.44882	0.11
Cold ischemia time	Hour	1.01642	0.99435	1.03897	0.15
Delayed graft function	**Yes**	**1.33374**	**1.03584**	**1.71731**	**0.026**
Recipient weight	Kg	0.9976	0.98728	1.00802	0.65
Preservation solution	Other	0.54839	0.22275	1.35009	0.19
Preservation solution	UW	0.83595	0.65002	1.07506	0.16

Table 34: Multiple Cox regression model after AIC-based backward selection for graft rejection in ESP and Control 1 (n=1206)

Risk factor	Category	Relative Risk	lower 0.95 CL	upper 0.95 CL	p-value
HLA mismatch Class II	**Per mismatch**	**1.21776**	**1.04323**	**1.42149**	**0.013**
Donor age	Year	1.01736	0.99512	1.0401	0.13
Delayed graft function	**Yes**	**1.5244**	**1.24302**	**1.86948**	**< 0,0001**
Donor SCr	10 µmol/l	1.00712	1.00331	1.01094	0.00024
Cold ischemia time	Hour	0.99341	0.97568	1.01146	0.47
Preservation solution	Other	0.99507	0.97735	1.01312	0.59
Preservation solution	UW	1.46721	0.91719	2.34706	0.11
Recipient diabetes	True	1.23328	0.97774	1.55561	0.077
Anti IL-2rAB	Yes	1.14544	0.93386	1.40495	0.19
Polyclonal AB	Yes	0.81514	0.62219	1.06793	0.14

7.4.8 Cox regression: rejections in ESP and Control 2

The relative risk for developing graft rejection estimated by Cox regression increased by 13% and 26% for each HLA class I mismatch and each HLA class II mismatch respectively. In this model, delayed graft function increased the risk of rejection by almost 60% (RR= 1.568; p < 0.0001). Interestingly, use of a preservation solution other than UW also increased the relative risk by 52% and the risk for recipients with diabetes was 1.24 fold higher than for patients without diabetes. Finally, this was the only analysis that showed a reduction in risk by 27% for rejection in patients receiving polyclonal antibodies for induction (Table 35).

Table 35: Multiple Cox regression model after AIC-based backward selection for graft rejection in ESP and Control 2 (n=1823)

Risk factor	Category	Relative Risk	lower 0.95 CL	upper 0.95 CL	p-value
HLA mismatch Class I	**Per mismatch**	**1.13222**	**1.04478**	**1.22698**	**0.0025**
HLA mismatch Class II	**Per mismatch**	**1.26631**	**1.10569**	**1.45026**	**0.00065**
Delayed graft function	**Yes**	**1.56841**	**1.31592**	**1.86935**	**< 0,0001**
Donor SCr	10 µmol/l	1.0007	1.00025	1.00115	0.0023
Cold ischemia time	Hour	0.99079	0.97621	1.00559	0.22
Preservation solution	**Other**	**1.52405**	**1.00782**	**2.30471**	**0.046**
Preservation solution	UW	1.03853	0.86465	1.24737	0.69
Recipient diabetes	**True**	**1.24178**	**1.01871**	**1.51369**	**0.032**
Anti IL-2rAB	Yes	0.96038	0.79693	1.15737	0.67
Polyclonal AB	**Yes**	**0.7303**	**0.5726**	**0.93141**	**0.011**

8   Strengths and Limitations of the analysis

In the present investigation, we were able to access the progress of the ESP to date by studying the <u>unique cohort of ESP patients transplanted from the beginning of the program in 1999 up to 2004.</u> We successfully collected additional information over and above the Eurotransplant database on 85% of the ESP patients and on two control groups, observed over the same time period as the ESP patients, and matching the ESP patients for donor age (Control 1) and recipient age (Control 2). The analysis consisted of 3400 patients, with a time of documented follow up comparable in all 3 groups indicating that there was no systematic error in the data capture and providing confidence about the robustness of the results.

Although the ESP prospectively allocates old donor organs to old recipients, it should be noted that this analysis is based mainly on data collected retrospectively. Certain information, in particular the long term data that was newly captured for this 5-year analysis was therefore only available for the "updated patient group", i.e. 85% of patients. Verification of Source data was only performed in selected cases and thus the number of outliers in the database is relatively high. Due to the nature of the program and the inclusion of ESP into ETKAS as of 2001 no perfect Control group could be defined. Control 1 differed in terms of recipient age, Control 2 differed in both recipient and donor age from the study group. Creatinine Clearance was calculated using the Cockroft-Gault Formula using baseline demographic data for weight, height and gender at time of transplantation. This limitation should be considered when interpreting the results. ESP does not restrict centres from transplanting patients with certain co-morbidity patterns or special pre-renal interventions, thus pre-transplant clinical condition accepted for transplantation within ESP may vary from centre to centre. The same applies to the donor. The ESP program does not restrict or stratify donor organs by co-morbidities such as diabetes or hypertension that are known to impact the quality of the organ and the graft function.   Centre-specific differences are already apparent when looking at the single centre results published to date. Differences in cold ischemic times, acute rejection rates, graft and patient survival rate have been reported. We did not account for these centre-specific differences in this analysis.

9 Discussion

The objectives of the ESP were to achieve a more efficient use of kidneys from elderly donors and to reduce the time that elderly patients wait for a kidney transplant. Overall, this 5 year analysis of the ESP shows that the aims of the program (see also 2.1.) were met. The availability of elderly donors increased from 169 (10% of all donors) in 1998 to 239 (almost 15% of all donors) in 2004. Simultaneously, the number of patients transplanted in the ESP increased from 227 in 1999 to 382 in 2003. The waiting time for elderly recipients transplanted within the ESP was reduced compared to the waiting time before introduction of ESP (Smits, et al., 2002). The cold ischemia time for ESP patients was significantly shorter with a mean of approximately 12 hours compared with over 17 hours in both control groups. Bearing in mind that the control groups differed in either donor or recipient age from the ESP groups, the main clinical outcomes in recipients of organs from donors age 65 or older were not negatively impacted by the ESP allocation. This will be discussed in more detail below.

Germany, Holland and Belgium were the largest contributors to the ESP and the two control groups, which compares well to the overall split of renal transplants performed within the Eurotransplant region (Doxiadis, et al., 2004). When considering the distribution of donor age, and because of its importance for interpreting outcome, it is worth highlighting that 50% of the donors in the ESP were above 70 years of age compared to only 3.7% of donors in Control 2. With an age of 67.7 years the average ESP recipient was 10 years older than a recipient in Control 1 and 4 years older than in Control 2. Interestingly, there were significantly more female donors in the ESP group (54.2%) compared to Control 2 (41.6%) while at the same time there were significantly more male recipients in the ESP group (64.8%) compared to Control 2 (60%). Differences in graft survival according to donor gender have been reported by Zeier et al. Death-censored actuarial renal allograft survival from female compared with male donors was worse in female recipients, and worse still in male recipients. The donor gender–associated risk ratio for graft loss was 1.15 in female recipients and 1.22 in male recipients (Zeier, et al., 2002). According to this report, the gender distribution in the ESP group might have been less favourable than in the other two groups. The incidence of diabetes and hypertension recorded in the medical history of the donor was highest in the ESP group, also reflecting a potentially less favourable starting point for

the ESP group. As expected from a much younger donor population the percentage of traumatic cause of donor death in the Control group 2 (any to old) was almost twice as high as in both ESP and Control 1. Eurotransplant evaluated the effect of different preservation solutions on the initial graft function and long term graft survival in two prospective randomized studies. They concluded that HTK is comparable to UW in its preservative abilities, whereas EC should be avoided (de Boer, et al., 1999). In all the groups, UW was the most commonly used preservation solution (62.2%), followed by HTK/Bretschneider (34.4%). In Control 2 UW was used even more frequently (66.9%) while HTK/Bretschneider was used more often in the ESP group (38.9%). Cox regression analyses performed in this 5 year analysis identified the use of a preservation solution other than UW and HTK/Bretschneider as an independent risk factor for patient survival that almost doubled the risk of death and was also associated with a 50% increased risk of rejection in the model for ESP and Control 2.

Prior to the ESP program, the waiting time for the older patients was significantly longer than for other age groups (Smits, et al., 2002). In the first year analysis the ESP group had already been shown to benefit as the median time on the waitinglist was now comparable at 3.94 years for ESP; 3.61 for Control 1 (old to any) and 3.89 for Control 2 (any to old). By the time of the five year analysis the waiting time for the ESP group had shortened further by 5 months, while the waiting time in Control 1 increased by 2.4 months and for Control 2 by one year. This trend for patients transplanted via ETKAS is in line with published reports regarding the increase in waiting time over recent years with over 21% waiting more than 5 years (Doxiadis, et al., 2004). The median waiting times for waitlisted patients older than 65 based on the OPTN data as of July 8, 2005 was comparable to the ESP patients with 3.67 years (Source: www.optn.org). 97% of the organs in the ESP program were, as expected, allocated locally or regionally, as compared to only 50% of the organs transplanted via ETKAS. This is about 10% less than the 61% locally or regionally transplanted organs in the ETKAS group for all ages since 1996 (Doxiadis, et al., 2004). However, one should bear in mind that ESP patients were included in ETKAS from 2001.

As Control 1 and 2 kidney transplants were allocated via an HLA-driven system, the median number of HLA-A,-B,-DR mismatches was significantly lower compared to the age-matched kidney transplants in the ESP group, 3 and 2 vs. 4, respectively. Not surprisingly, the number of class I (HLA-A&B) and class II (HLA-DR) HLA-mismatches was significantly higher for the ESP group as well. 99.7% of ESP patients had at least 1

class I and 92.9% at least 1 class II mismatch. In comparison, within the whole of ETKAS a steady decrease in the number of 0-2 mismatch transplants and an increase in the number of 3-6 mismatch transplants is observed (Doxiadis, et al., 2004). The trade-off between immunological and non-immunological risk factors was taken into account before implementation of the ESP (Smits, et al., 2000). It had been postulated that the HLA matching effect in kidney transplantation is decreasing in donors above 40 years of age (Cicciarelli, et al., 1999). Furthermore, as HLA compatibility was disregarded in ESP, the program was restricted to non-immunized (PRA <5%) recipients who were awaiting their first transplant. In our ESP analysis population, 22 out of 1405 patients (1.6%) were highly sensitized, the remaining 98.4% complied with the ESP rule. In both of the control groups the number of highly sensitized patients was significantly higher at approximately 10% which is comparable to the overall ET population (Doxiadis, et al., 2004). Also, a prerequisite of the program was to reduce the cold-ischemia time as far as possible by allocating organs locally to minimize the accumulation of risk factors and hence improve the outcome in these recipients. Although median cold-ischemic times were significantly lower in the ESP group compared to the controls (p<0.001), only 50% of the ESP transplants had a cold ischemia time of < 12h and only 26% < 8 hours. Compared with the first year analysis, it became apparent that the cold ischemia time for all three groups had been successfully reduced, and differences between groups had become smaller. Reduction of non-immunologic damage by ensuring a short CIT is considered important by several groups to counterbalance possible immunologic effects on graft function, especially in the old-for-old setting (Klehr, et al., 1996; Lee, et al., 2000; Preuschof, et al., 1991; Shoskes and Cecka, 1997). A single centre ESP publication (Giessing, et al., 2003) reported very short CIT in the ESP group (8.3 hours) compared to other ESP reports (Smits: 12 hours (Smits, et al., 2002), Schlieper: 13.3 hours (Schlieper, et al., 2001), Beckurts: 9.5 hours (Beckurts, et al., 2001)). The author strongly believes that the good graft function (only 12 % DGF compared to 29.7% in the ESP group as a whole) and graft survival observed were driven to a great extent by this reduction of CIT. On the other hand, Opelz data based on the CTS registry suggests that a very short CIT (< 6 hours) may not be advantageous, and that only a CIT > 24 hours has a negative impact on graft survival. He showed that HLA matching had a highly significant impact even when the analysis was restricted to patients with an ischemia time between 0-12 hours (Opelz, 2002). In this analysis, despite many of the baseline characteristics of the ESP group

being less favourable, these appear to have been successfully balanced by the ESP program, at least in the short term, as evidenced by the fact early graft function was as good as Control 2 and significantly better than Control 1.

The ESP (old to old) group had the lowest 1 and 5 year <u>patient survival</u> rates with 86% and 60% compared to 88% and 71% for Control 1(old to any) and 90% and 74% for Control 2 (any to old),as determined by Kaplan Meier Analysis, respectively. The OPTN database reported an unadjusted 5-year survival of 65.2% in recipients older than 65 years of age and 78% in recipients age 50-54 (Source: <u>www.optn.org</u>). Meier Kriesche reported a 1-year survival of 81% in recipients aged 60 and above (Meier-Kriesche, et al., 1999). Fritsche and Arbogast reported similar 1 year patient survival for a subgroup of the ESP patients while a nation wide analysis from Israel reported a lower 1 year survival rate of only 54% in the old to old population (Arbogast, et al., 2005; Fritsche, et al., 2003; Weiss-Salz, et al., 2005). The results for Control 1 are, as expected, in line with what has been published by Eurotransplant, and survival rates for Control 2 are also comparable to what was published by Fritsche at al. (Fritsche, et al., 2003; Smits, et al., 2002). Differences between groups could be explained by risk factors such as recipient gender, delayed graft function, donor age, graft loss, recipient diabetes, a preservation solution other than UW and HTK/Bretschneider and cardiovascular disease in the medical history of the recipient. Interestingly, DGF increased the risk of death by 40% and use of a preservation solution other than UW and HTK/Bretschneider almost doubled the risk of death in one of the analyses. This finding is certainly interesting, but it is supported by a relatively small number of cases in which none of the two main solutions was used. Further evaluations should be considered before a specific recommendation can be given regarding the avoidance of specific preservation solutions. Maintaining short ischemia times or even further reducing them seems to be important in order to decrease the incidence of DGF further. Advocating the use of UW for preservation should also be considered. Of great importance is also the result of the <u>sub-analyses for Control 2</u> split in donors age < and ≥ 60 years of age and the subsequent model extrapolated to simulate the survival for Control 2 with a donor and recipient age comparable to the ESP group. These analyses were performed to account for the differences in both donor as well as recipient age between ESP and Control 2. Both analyses showed that the <u>patient survival</u> for the Control 2d≥60 as well as for the Control 2 extrapolated to ESP parameters was not different form the survival of the ESP

group, strongly suggesting that the age of the donor is the main variable driving differences in survival between ESP and Control 2.

Uncensored graft survival in ESP (75% at 1 year and 47% at 5 years post- transplant) was comparable to Control 1 (74% at 1 year and 51% at 5 years post-transplant) but significantly less than Control 2 (83% at 1 year and 64% at 5 years post- transplant). However, the difference in graft and patient survival between ESP and Control 2 disappeared if Control 2 was restricted to donor age ≥ 60. This demonstrates the impact of donor age on long term outcome and suggests the ESP concept was successful in optimizing the outcome when compared to a similar population transplanted via ETKAS. The fact that Control 1 showed a similar graft and patient survival compared to the ESP group, despite the average age of the recipient being 10 years younger, might suggest that an old organ transplanted into a younger recipient might actually negatively impact the outcome of the younger recipients. This finding is in line with results published by Waiser who found the "old to young" transplants to have the poorest graft survival (approximately 50% at 5 years, see also page 22). Cox regression models as well as analysis of Control 2 d ≥ 60 and extrapolated Control 2 showed results similar to those for the survival analysis with DGF and male gender of the recipient being strong independent risk factors and no significant differences when restricting Control 2 to a more similar donor age.

Death censored graft survival in ESP was not different from Control 1 (1 year: 83% vs. 81% and 5 year: 67% for both), but significantly different from Control 2 (1 year 90% and 5 year 81%). The one year graft survival rates reported by Fritsche for a subpopulation of the ESP and Control 2 are almost identical; however their results were not statistically significant (Fritsche, et al., 2003). The increased size and duration of follow-up in this evaluation is the most likely explanation for the difference becoming significant. The most important insight from this analysis is that the old donor kidneys did not survive longer in a younger recipient (Control 1 old to any) despite the fact they had less HLA mismatches and fewer rejections. Hariharan and colleagues suggested in 1997 that older donor kidneys have a better graft survival when transplanted into older recipients compared to younger recipients (Hariharan, et al., 1997). The fact that kidneys from younger donors survive longer is not surprising. In addition, differences between death censored graft survival in ESP and Control 2 could be explained by

differences in recipient gender and DGF, but interestingly also by HLA class I mismatches. For every mismatch in class I antigens, the risk of graft loss increased by 15%.

Results published by Waiser et al. showed that graft survival of kidneys from old donors was significantly reduced in young recipients compared to oldones. <u>Graft loss</u> in the "old to young" group was mainly due to acute and chronic rejection (Waiser, et al., 2000). Interestingly, similar results were found in this analysis with patients in Control 1 (old to any) having lost more grafts due to rejection (42.4%) compared to ESP (old to old 29.5%) or Control 2 (any to young, 28.8%). A cumulative effect, as a result of damage due to ischemia/reperfusion and the reduced capacity of kidneys from older donors to respond to physiological and pathological stresses might explain this phenomenon (see also 1.1.1.1). While Meier-Kriesche suggested that donor age represents a significant risk factor for <u>patient death with a functioning graft</u> - speculating that worse clearance of the aged graft translates into hypertension in a younger recipient or represents an intrinsic a risk factor for patient survival (Meier-Kriesche, et al., 2002) - the current analysis did not show a significant difference between the three groups. Overall, of the total numberof patients who died, 76.6% had functioning grafts. It is worth mentioning that the definition and selection of marginal donors in the US and Europe are quite different. In the US expanded donor criteria (ECD) are defined as all donors older than 60 years and donors older than 50 years with any 2 of the following criteria: (a) hypertension; (b) cerebrovascular cause of brain death; or (c) donor SCr > 1.5 mg/dl (Stratta, et al., 2004), while no clear definition exists in Europe (Tullius, et al., 2001). However, published data, as well as this report suggests that the quality of organs accepted for transplantation is much lower in Europe as compared to that in the US. This needs to be taken into account when comparing results from Europe and the US.

Occurrence of serious <u>opportunistic infections</u> at any time post transplant was very common and highest in ESP (51%) and Control 1 (50,4%) patients compared to 38,8% in Control 2. Overall, <u>cardiovascular events</u> (defined as MI, bypass grafting, stroke or amputation) and malignancies at any time post transplant were reported in 14,3% and 9,5% of all patients, again with the highest incidence in the ESP group (15,2% and 10,3 % respectively). Almost 60% of all patients who died did so as a result of an infectious or cardiovascular event. <u>Infectious death</u> occurred in approximately 30% in all three

groups

(no significant difference). Interestingly death due to cardiovascular events occurred slightly less often in the ESP group (22,9%) as compared to Control 1 (32,4%) and 2 (32,5%). In 2001 Meier-Kriesche showed both deaths related to infections but also mortality secondary to cardiovascular disease increases progressively with increasing age of the recipient (Meier-Kriesche, et al., 2001). The finding of equal percentages of patients with infectious death in all three groups, even in Control 1 with a much younger average age of the recipient, is somewhat surprising and suggests a potential impact of the older donor organ (Martins, et al., 2005). The higher incidence of impaired graft function or higher levels of imunosuppression associated with a higher acute rejection rate might help explain this finding.

As mentioned previously a success of the local allocation and the shorter ischemia time is reflected in the significantly higher percentage of initial function, the reduced rate of DGF and the lower SCr values in the ESP group compared to Control 1. Figure 17 impressively shows that the ESP pattern for early function was almost identical to Control 2 where the donor organs were on average 20 years younger. Delayed graft function was seen in 29,7%; 36,2% and 30,9% of the ESP, Control 1 and Control 2 transplants respectively. The ESP single centre analysis by Giessing reported a DGF rate of only 12% as opposed to a significantly higher incidence in the controls (43%). Voiculesco (Voiculescu, et al., 2002), whose ESP study group had a CIT of more than 12 hours, reported delayed graft function in 64% of patients. The first year data published by Smits (Smits, et al., 2002) showed a 33% incidence of DGF with a mean CIT of 12 hours. With DGF being an independent risk factor in almost all our models for patient survival, censored and uncensored graft survival and acute rejection one argument in favour of the ESP is reconfirmed.

The preliminary analyses of the ESP that were published prior to this update already reported a higher rate of acute rejections in the ESP group (around 40%; (Giessing, et al., 2003; Schlieper, et al., 2001; Smits, et al., 2002; Voiculescu, et al., 2002) compared to Control 1 (30% (Smits, et al., 2002)) and Control 2 (27.4% (Fritsche, et al., 2003)). In general the acute rejection rates for all groups reported in the 5 year database appear to be lower than expected from the initial reports. One reason could be that acute rejection was under reported. However, the ESP group still had significantly higher

rates of acute rejection, biopsy proven acute rejection, early and late rejection despite the fact that more than half of the patients received antibody induction therapy and 84% of the ESP patients were maintained on triple immunosuppression, highlighting the immunologic capacity even of aged recipients. Experimental data in a rat model support an enhanced cellular response in elderly recipients leading to accelerated chronic graft rejection (Pascher, et al., 2003). The high number of immunologic responses raises concerns about how effectively a shorter CIT counterbalances HLA mismatching in the ESP setting (Giessing, et al., 2004). However, long term outcome did not seem to be negatively affected and in fact, a much higher incidence of graft loss due to rejection was found in Control 1.

Cox regression analysis partially explained the differences in acute rejection rates between ESP and Control 2. Class I and II HLA mismatches were identified as significant independent risk factors increasing the risk of acute rejection by 32% and 26%. Patients with DGF had a 57% increased risk. One could speculate if the risk for acute rejection associated with HLA mismatching could be overcome by using more intense immunosuppression, or at least a higher initial immunosuppression (de Fijter, 2005; Reutzel-Selke, et al., 2005). However, this must be balanced by the finding that the incidence of infectious complications and death secondary to infection is already very high in the ESP group. Another option would be to try and achieve better HLA matching while maintaining the same CIT. This could be achieved if allocation remained restricted to local recipients but HLA matching was used instead of waiting time as an allocation criterion (Fritsche, et al., 2003).

Although statistically significant, the difference of 2 days in the median number of in-hospital days for transplantation for ESP and Control 1 (27 days) compared to Control 2 (25 days) does not seem to be clinically relevant. However, when looking at readmissions and length of hospital stay during any readmission, the ESP patients appeared to experience more complications and require slightly longer hospital care than the control groups. The fact that the clinical condition at the most recent visit was judged by the treating physician as poor for 20,1% of ESP patients compared to 12,9% of patients in Control 1 and 10,1% of patients in Control 2 also indicated that ESP patients faced more problems than patients in the control groups.

Isolated from any ethical concerns, an elderly patient awaiting renal transplantation might be biased towards wanting to wait for an organ from a younger donor. However, the benefit of transplantation for these patients has to be looked at in comparison to risk

of death on the waiting list. Wolfe et al. determined that renal transplantation doubles the life expectancy of a patient on dialysis listed for transplantation in the United States. Among patients who were 60-74 years old, the cumulative survival rate improved after the first year, with a projected increased life span of five years and a decrease in the long term risk of death of 61 percent (Wolfe, et al., 1999). In amore recent analysis from Europe, Oniscu and colleagues confirmed that despite an initial higher risk of death, long-term survival for patients who undergo transplantation is significantly better compared with patients who are listed but remain on dialysis. A successful transplant triples the life expectancy of a listed renal failure patient. In patients aged 65 years or older, transplantation lead to a twice-longer life expectancy compared with dialysis, with this proportional increase being greater than that noted in patients aged 18 to 34 years (Oniscu, et al., 2005).

10   Conclusions

Based on the findings of this analysis and results reported by other authors it can be concluded that the objectives of the ESP have been met and the program is beneficial for kidney transplantation candidates, in particular for elderly ones, but in general also for the entire group of waiting list patients. The main reasons are:

1. The program led to an increased availability of elderly donors from 169 (10% of all donors) in 1998 to 239 (almost 15% of all donors) in 2004.

2. The waiting time for elderly recipients transplanted within the ESP was decreased by 5 months over the course of the analysis, while the waiting time via ETKAS in Control 1 increased by 2,4 months and for Control 2 by one year over the same period of time. As a result, the ESP group is currently the group with the shortest waiting time.

3. The cold ischemia time for ESP patients was significantly shortened with a mean of approximately 12 hours compared with over 17 hours in both control groups. This translated into a significantly higher percentage of initial function, a reduced rate of DGF and lower SCr values at all timepoints in the ESP group compared to Control 1. Maintaining short ischemia times or even reducing them further seems to be important in order to minimize the incidence of DGF that was shown to be a strong independent risk factor for patient survival, censored and uncensored graft survival as well as acute rejection.

4. The main clinical outcomes in recipients of organs from donors age 65 or older were not negatively impacted by the ESP allocation. Donor age is the main variable driving differences in survival between ESP and Control2. Old donor kidneys did not survive longer in a younger recipient.

From the analysis of risk factors and clinical outcomes performed in this investigation, certain recommendations to improve the program can be given. In particular, using HLA matching should be considered instead of waiting time as an allocation criterion. In fact, results point to an effective immune response even in old recipients (more rejections despite adequate therapy) and at the same time a high incidence of infection-related complications, limiting the room for increased immunosuppression. The identification of specific immunosuppressive treatments for elderly patients and a comparison of clinical outcomes of transplanted and non-transplanted elderly patients are among the most relevant topics future research could address.

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Appendix

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Eidestattliche Erklärung

„Ich, Jana Nöldeke, erkläre, dass ich die vorgelegte Dissertationsschrift mit dem Thema: **„Five Year Update of the Eurotransplant Senior Program"** selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe."

Berlin, den 3. August 2005   Jana Nöldeke