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The golden years

Pippias, M.

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Chapter 1

Introduction, aims and outline of this thesis

Once an individual has reached end-stage renal disease (ESRD) the kidney is no longer able to function at a level required to sustain life. For those with ESRD there is the option of commencing renal replacement therapy (RRT) in the form of either dialysis (haemodialysis or peritoneal dialysis) or a kidney transplant. Though termed 'replacement therapy' neither of these treatments replace the kidney function by 100%; as such, individuals receiving RRT have a shorter life expectancy than the general population (1). The life expectancy for a 40-year-old person in the general population is 42.2 years, whereas it is 26.5 years for a 40-44-year-old transplant recipient, and just 11.9 years for a 40-44-year-old receiving dialysis (2). Not only do individuals receiving dialysis have a shortened life expectancy compared to kidney transplant recipients, they also have a lower quality of life (3). Therefore, given the option, most individuals would prefer a kidney transplant over dialysis.

Kidney transplantation in the 21st century

Kidney transplantation began in earnest in the 20th century, with the first human-to-human kidney transplants occurring in 1936 in Ukraine. Unfortunately, these early kidney transplants, performed in an effort to overcome the effects of mercury poisoning, proved unsuccessful. Breakthroughs in the technical aspects of vascular anastomosis and appropriate positioning of the kidney, alongside the understanding of the workings of the immune system (4) propelled this experimental technique forward into the realms of reality. In 1954, the first successful kidney transplantation took place in Boston, United States (US). Joseph Murray's team overcame the obstacle that is the immune system, by avoiding it altogether; the donor and recipient pair were identical twins (5). Unfortunately the transplant failed eight years later due to the recurrence of glomerulonephritis, the condition that had caused the patient's own kidneys to fail.

Prior to the 1960s kidney transplantation had relied entirely on either identical twin transplantations or total body irradiation in order to eradicate the immune system (a technique that cost more lives than it saved). The introduction of the first chemical immunosuppressants in the 1960s was heralded as the dawn of a new era in transplantation (6). Despite the introduction of these immunosuppressive agents, kidney graft survival remained poor, with one-year graft survival of just 40% (7). In the 1980s and 1990s the addition of new, potent immunosuppressants, along with advances in crossmatching techniques and organ procurement strategies further revolutionised this field. By the end of the 1990s one-year patient and graft survival was 95-97% and 89-94% respectively (8).

Today, medical professionals continue to push the limits of kidney transplantation. Whereas previously transplantations across blood groups (ABO incompatible) and human leucocyte antigen (HLA) incompatible transplants where certain routes to

graft failure, they are now performed on an almost routine basis. Currently, one-year patient and graft survival is 98-99% and 92-96% respectively, whilst five-year patient and graft survival is 92-95% and 81-87% respectively (2). Although short-term patient and graft survival outcomes have greatly improved since the 1990s, medium- to long-term outcomes have not improved at the same rate (8, 9). Though kidney transplantation has proved an effective treatment for ESRD, it is as of yet, by no means a cure.

Who should receive a kidney transplant?

As kidney transplantation has evolved from an experimental to a routine procedure, so have the eligibility criteria for transplantation evolved. In the early days, kidney transplantation was limited to young (under 40 years) and relatively healthy individuals. With each passing decade the upper age limit for kidney transplantation was extended (10-12). By 2012, the median age for kidney transplantation in 34 countries across Europe was 51.9 years, with a substantial variation between countries; ranging from 38.7 years in Bosnia and Herzegovina to 57.0 years in the Spanish region of Asturias (13). As with the general population, the RRT population is aging; the median age of a patient commencing RRT in Europe is currently 63.0 years, though again this ranges from 48.1 years in the Ukraine to 70.6 years in Dutch-speaking Belgium (2). As the RRT population ages it is likely that an increasing number older adults will wish to consider a kidney transplant. Although the majority of kidney transplant guidelines do not have an upper age limit cut off per se (14-16), questions are being raised as to whether individuals of all ages should be eligible for transplantation.

Who should donate a kidney?

Alongside the evolution of transplantation medicine, national organ allocation algorithms have evolved (17). These complex algorithms have one overriding goal; to match the potential longevity of the available donor kidney with the potential longevity of the recipient (utility) in an equitable manner that ensures fair access to transplantation for all potential recipients.

As a consequence of loosening the eligibility criteria for kidney transplantation, an increasing number of individuals are listed on the transplant waiting list. The demand for viable kidneys for transplantation far exceeds supply (Figure 1.1). This disparity between organ availability and the growing demand for transplantation has compelled medical professionals to re-think the definition of what is a suitable deceased donor. As with transplant recipients, whilst previously one would question the suitability of a deceased donor aged >45 years (18), one is now questioning the suitability of a deceased donor aged >75 years (19). As a consequence of using older (more marginal) deceased donor kidneys

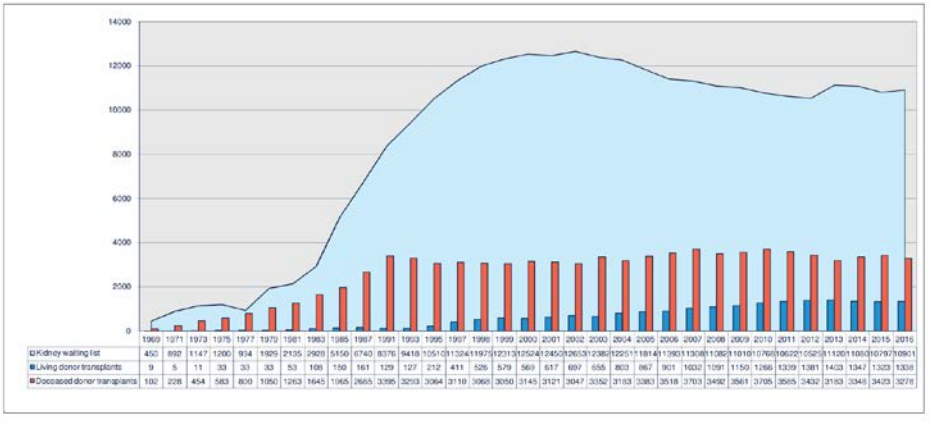


Figure 1.1. The dynamics of the Eurotransplant kidney transplant waiting list and transplants between 1969 and 2016. Figure reproduced (with permission) from Eurotransplant 2016 Annual Report (20). Red bars signify the number of deceased donor transplants that year; blue bars signify the number of living donor transplants that year; and the shaded light blue area the number of people registered on the kidney transplant waiting list that year. Data is for the Eurotransplant region. This region consists of a number of countries, the exact composition of which has increased over time. See the Eurotransplant 2016 Annual Report (20) for a description of which countries were active per year.

the median age of deceased donors in many European countries has risen from 36 years in 1990 to 54 years in 2016 (20).

Older deceased donor kidneys and marginal donor kidneys in general have a shorter survival potential than younger deceased donor kidneys. Therefore longevity matching the potential recipient with the potential deceased donor kidney is performed; predominantly by age matching the potential pair. However as demand for these better quality and younger kidneys exceeds supply, it is not possible to continue providing the best quality kidneys to younger recipients. Some advocate 'better a small fish than an empty dish' i.e. it is preferable to have a poorer quality deceased donor kidney than to remain on dialysis (21). Others advocate that given that the first year of transplantation is associated with a higher risk of patient death compared to remaining on dialysis (given that transplantation is a major surgical procedure with risks inherent to surgery), it is better to remain on dialysis and await a better quality kidney. In order to help solve this conundrum the survival outcomes of donor-recipient pairs of different ages need to be reassessed in the current transplant era.

Of course deceased donors are not the only source of donor kidneys; living donors provide

a valuable supply of kidneys for transplantation. Within Europe, the success of living kidney donor programmes varies considerably (22). Whilst living kidney donor transplant survival outcomes are on the whole better than deceased donor transplant survival outcomes (1), for most European countries the rate of living donor transplantation is significantly lower than those of deceased donor transplantation (1). One of the overriding concerns within living donor transplant programs is that a healthy individual is undergoing a major surgical procedure, predominantly for the benefit of someone else. As such clinicians have an overriding duty to ensure the long-term risk of ESRD and of survival in general of a potential living kidney donor remains below an acceptable threshold of risk.

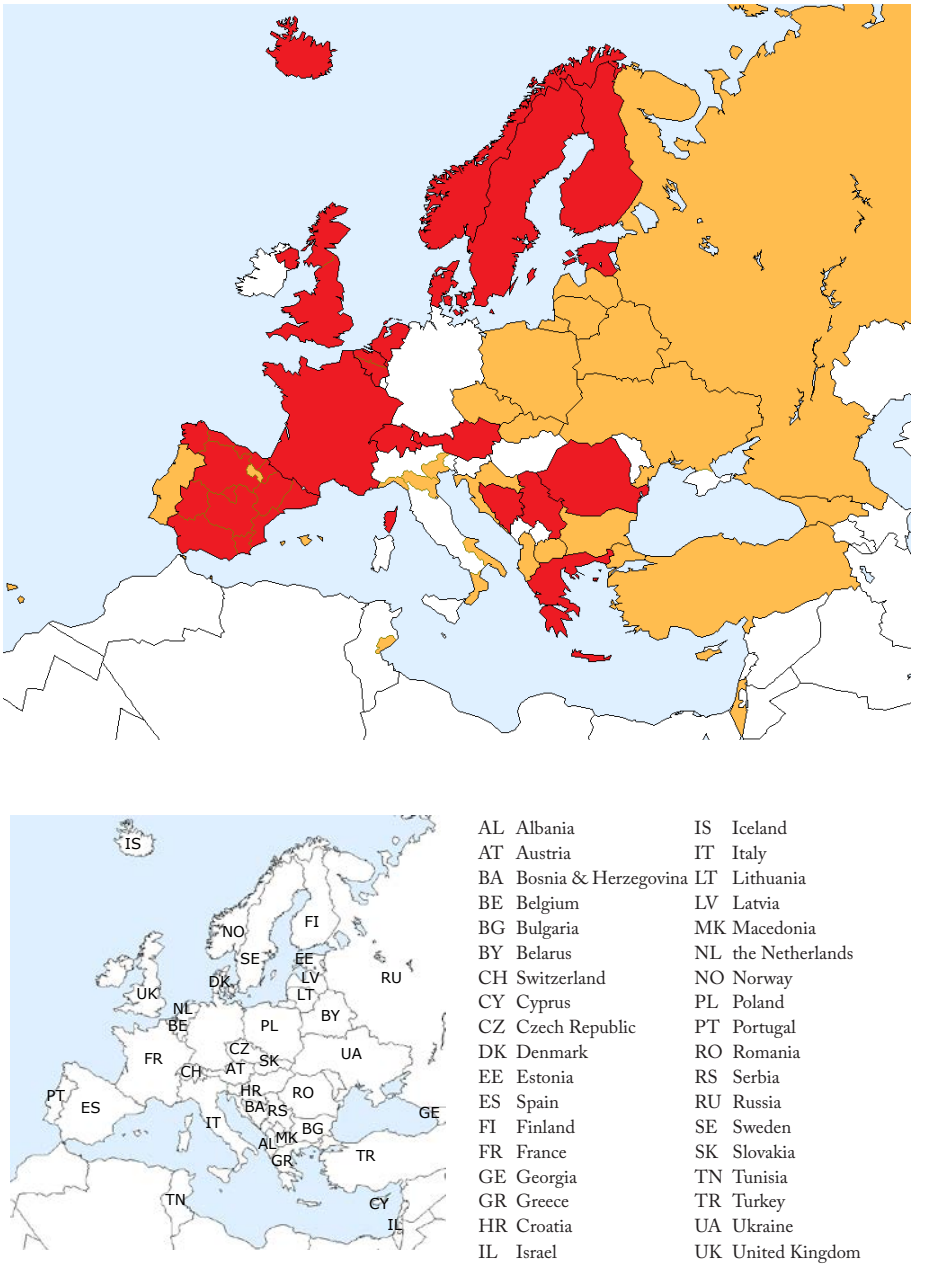
The ERA-EDTA Registry

The bulk of the data presented in this thesis was obtained from the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Registry (23). The ERA-EDTA Registry was founded in 1964 and is currently based at the Academic Medical Center, Amsterdam, the Netherlands. On an annual basis the ERA-EDTA Registry collects data from the national and regional renal registries across Europe and in countries bordering the Mediterranean Sea. In 2017 data was collected for the 2015 Annual Report (2). This report contained data from 52 national or regional renal registries in 36 countries, covering 65.4% of the European population (Figure 1.2). The duration with which the Registry has been functioning for and the size of the Registry database (over 770,000 patient records) allows for the epidemiology of RRT in Europe to be examined over a considerable time period, in addition, it allows for rare diseases to be examined.

Objectives

The research reported in this thesis aims to examine kidney transplant survival outcomes in the current European transplant era. This is to be achieved by:

1. Providing an overview of the current epidemiology of RRT in Europe, with a particular focus on the older adult receiving RRT.
2. Examining the trends in the quality of deceased donor kidneys over the past ten years and the effects these older deceased donor kidneys have on survival outcomes.
3. Examining the current evidence pertaining to post-donation pregnancy risk in living kidney donors, whether living kidney donor guidelines are based on this evidence and whether there is consistency between the published guidelines.
4. Examining the kidney transplant survival outcomes by primary renal disease.



AL	Albania	IS	Iceland
AT	Austria	IT	Italy
BA	Bosnia & Herzegovina	LT	Lithuania
BE	Belgium	LV	Latvia
BG	Bulgaria	MK	Macedonia
BY	Belarus	NL	the Netherlands
CH	Switzerland	NO	Norway
CY	Cyprus	PL	Poland
CZ	Czech Republic	PT	Portugal
DK	Denmark	RO	Romania
EE	Estonia	RS	Serbia
ES	Spain	RU	Russia
FI	Finland	SE	Sweden
FR	France	SK	Slovakia
GE	Georgia	TN	Tunisia
GR	Greece	TR	Turkey
HR	Croatia	UA	Ukraine
IL	Israel	UK	United Kingdom

Figure 1.2. National and regional registries contributing data to the ERA-EDTA Registry in 2015. Figure reproduced (with permission) from the ERA-EDTA Registry 2015 Annual Report (2). Countries/regions highlighted in red contributed individual level data, whereas countries highlighted in orange contributed aggregated data. No data was available in 2015 from the countries or regions in white.

Outline of this thesis

The first section of this thesis provides *An overview of RRT in Europe*. **Chapter 2** provides the age and sex-specific estimates for the lifetime risk of requiring RRT for ESRD across ten European countries. **Chapter 3** provides a summary of the incidence, prevalence, transplantation rates and survival of patients receiving RRT in Europe in 2015. **Chapter 4** provides an update of the trends in the incidence, prevalence, and survival of patients receiving RRT in Europe between 1998 and 2011, with a particular focus on adults aged >65 years.

The second section of this thesis is titled *Transplantation in the 21st century: the older recipient, the older donor and the living donor.* The first two chapters of this section focus on the older recipient. **Chapter 5** provides an overview of the epidemiology of RRT for patients aged >65 to 74 years and those >75 years in Europe in 2012. Building on from this overview, **Chapter 6** examines the access to kidney transplantation, the allocation of kidneys to, and the survival of patients aged ≥75 to 84 years receiving RRT between 2005 and 2014 in thirteen European countries.

The deceased donor is the focus of chapters 7 to 9. **Chapter 7** investigates trends in the quality of transplanted deceased donor kidneys between 2005 and 2015 using the kidney donor risk index (KDRI) as a marker of kidney quality (24). Chapters 8 and 9 examine the survival outcomes of older deceased donor kidneys from differing perspectives. **Chapter 8** examines the impact of the older deceased donor kidney on the survival outcomes in younger and older recipients, whilst **Chapter 9** examines the survival outcomes of young recipients receiving either young or old deceased donor kidneys. In **Chapter 10** the focus turns to the living donor; in this chapter the evidence pertaining to pregnancy outcomes in living kidney donors is examined, and the consistency between national and international guidelines discussing the issue of pregnancy post-kidney donation is reviewed.

The final section of this thesis is titled *Treatment outcomes in different primary renal diseases*. **Chapter 11** focuses on the long-term kidney graft survival in transplant recipients with a primary renal disease of primary glomerulonephritis (GN) and determines if the risk of kidney graft loss in those with primary GN differs between living and deceased donor kidneys. **Chapter 12** examines the survival outcomes of transplant recipients with a primary renal disease of scleroderma.

Chapter 13 provides a general discussion of this thesis and recommendations for future research. In **Chapter 14** all findings are then briefly summarized in English and in Dutch.