The golden years

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Chapter 13

General Discussion & Future Perspectives

Kidney transplantation is promoted as the best treatment modality for individuals with ESRD in need of RRT, both in terms of life expectancy and quality of life. Yet kidney transplantation remains a treatment for ESRD with its own associated risks and complications and is by no means a cure. Outcomes research is a continuous process where regular updates are required to enable state-of-the art treatment. Given that the field of transplantation medicine is continually changing, with outcomes varying across countries and continents, one cannot base treatment options on data which may be out of date or non-specific to the individual in question.

The research reported in this thesis aimed to examine kidney transplant survival outcomes in the current European transplant era. This was to be achieved by firstly providing an overview of the current epidemiology of RRT in Europe, focusing particularly on the older adult receiving RRT. Secondly, by examining the trends in the quality of deceased donor kidneys over the past ten years and the effect of older deceased donor kidneys on transplant survival outcomes. Thirdly, by examining the current evidence pertaining to post-donation pregnancy risk in living donors, whether living kidney donor guidelines are based on this evidence and whether there is consistency between guidelines. Finally by examining the kidney transplant survival outcomes in specific primary renal diseases. In this chapter the main findings from this research and their implications for clinical practice and future transplant research are discussed.

An overview of RRT in Europe: the older adult with ESRD

We showed that after years of constant growth, the incidence of RRT in 2011 across eighteen European countries began to decline. Does this decline in the incidence of RRT mean that we are now effectively treating CKD? The incidence of RRT has probably in part, declined due to better management of the underlying diseases responsible for CKD such as diabetes mellitus and in part, due to better management of CKD thereby avoiding or at least delaying the progression to ESRD. Unfortunately the limited number of CKD registries makes it more difficult to truly determine the prevalence and progression of CKD, nevertheless cross-sectional and cohort studies to this effect have been successfully performed (277, 278).

In our study the stabilisation in the incidence rate seen between 2001 and 2011 in older adults aged ≥75 years, may well be due to the increased consideration for not starting RRT too soon or at all and instead instigating conservative care therapy. Conservative care therapy has been formally introduced as a treatment option for patients with ESRD in multiple countries. However its uptake varies considerably (46, 279, 280).

Many predictions regarding the impact of an aging population on RRT services

are not being entirely realised; it was long suspected that as the life expectancy of the general population increased, the burden of RRT would also increase. Peters et al. recently examined this concept in eleven European countries (281). They found that indeed, living longer coincided with an increased prevalence of adults aged ≥75 years receiving RRT, to the extent that a 1-year increase in life expectancy was associated with an approximately 20% increase in RRT prevalence (281). However, after adjustments were made for example to country GDP, the association decreased to approximately 11% in men and became statistically insignificant amongst women.

In Europe the country differences in the incidence of adults aged ≥75 years initiating RRT are striking. In Chapter 5 we report that the proportion of incident RRT patients aged ≥75 years varied from a sixth of the incident population (15%) in Romania and Serbia to just under half of the incident population in Dutch-speaking Belgium (44%) and Greece (44%). Helve et al. reported a six-fold difference in the incidence of RRT in this age group, whereas amongst those aged 20 to 74 years there was only a two-fold difference (282). They were unable to find any plausible explanations in terms of country wealth, life expectancy, co-morbidities or other patient characteristics to account for these differences. We also found a substantial country level variation in this age group in access to transplantation. The treatment options for older adults aged ≥75 years with ESRD seem to vary substantially throughout Europe.

Transplantation in the 21st century: the older recipient, the older donor and the living donor

Allocation algorithms have one overriding goal; to match the potential longevity of the available donor kidney with the potential longevity of the recipient, in an equitable manner which ensures fair access to transplantation for all potential recipients, whilst at the same time reducing the organ discard rate. This is without doubt, a balancing act between the ethicist and the mathematician, the idealist and the pragmatist and between the philosophical concepts of justice and utility.

The older recipient

In Seattle, US in the 1960s during the emergence of dialysis as a treatment for ESRD a committee was established to decide who was eligible for this potentially lifesaving but extremely expensive and limited resource (283, 284). The 'God squad' as they were eventually named by the press, allocated this emerging treatment to those deemed to have the highest 'societal worth'. The lucky few chosen patients were all under the age of 45 years without any co-morbidities, even those with a diagnosis of hypertension were excluded. The RRT population is now very much older (1), has multiple co-morbidities (285) and

is ethnically diverse (286). Whilst within the world of dialysis, the perception of who is eligible for treatment has dramatically shifted with time, within the world of kidney transplantation, perceptions are moving at a somewhat slower pace. Clinical practice guidelines do not restrict kidney transplantation on age alone (14, 15, 287). Despite this in Chapter 6 we report on a substantial country level variation in access to transplantation in older adults aged >75 years receiving RRT. In 2014 this varied from 0% of the prevalent adult dialysis population in Greece to almost 4% in Norway. Whist at the same time the older adults aged >75 years made up almost a third of the prevalent adult dialysis population in Greece (30.3%) and Norway (28.5%). From these results the ethicist may well conclude that 'justice', that is, equal access to transplantation for all, is not particularly well practiced with regards to this age group. It must be remembered though that we only have access to transplantation data and not to waiting-list data, therefore we cannot from our studies determine if there is indeed equal access to referral to the waiting-list for all ages, though it is likely that the older adult patient does not have equal access at this point in the process either. There are many reasons, both known and unknown that may explain the low and varied access to kidney transplantation in this age group. It could be that differences across European countries may be due to cultural (both medical and societal) attitudes to the older adult (288). To this effect, the European Union funded EDITH project which amongst other aims is identifying the influencing factors on the choice of treatment modalities by both patients and doctors across Europe may shed some light on this matter (289).

The philosophical concept of utility, is one where the allocation of organs is directed to those who will derive the greatest benefit from them. In Chapter 6 we report that the seven-year unadjusted patient and graft survival probabilities for transplant recipients aged 75 to 84 years were 49.1% (95% confidence interval, 95%CI: 43.6; 54.4) and 41.7% (95%CI: 36.5; 46.8) respectively, with a temporal trend towards improved survival outcomes. These were outcomes of kidneys from predominantly older deceased donors with a median age of 67 years in 2005 increasing to 77 years by 2015. In Chapter 8 we present survival outcomes of recipients aged 40, 50 or 60 years receiving a deceased donor kidney (median donor age of 60 years). The ten-year cumulative risk of graft failure for these recipients were approximately 40%, 46% and 50-60% respectively. It is clear to see from all these outcomes that the younger the recipient the better the post-transplant survival outcome. Therefore one may consider that utility is not fulfilled in the older adult age group and that if the concept of utility were to be fully implemented then we would conclude that organs for transplantation are better suited in younger recipients where the most use from them will be derived. However the concept of 'greatest benefit' is not clear

cut. Does greatest benefit relate to patient survival, or graft survival, or quality of life, or life years gained, or societal benefits? Who decides on what the definition of 'greatest benefit' should be?

The benefits of kidney transplantation in terms of quality of life gained should not be underestimated. A 2016 literature review and position statement by the ERA-EDTA Descartes working group and the European Renal Best Practice reported that both survival and quality of life are superior in older adult transplant recipients compared to those remaining on dialysis (16). In addition by means of a literature review Huang et al. add that despite an increase in mortality, graft failure censored for death is comparable between older adult and young transplant recipients (290). Furthermore they conclude that both older adults and younger recipients have similar relative benefits from transplantation but life expectancy is greater in younger recipients. Based on these outcomes the idealist would argue that given the need for justice within the world of transplantation and the improved survival outcomes, older adult transplant recipients should be offered access to the kidney transplant waiting-list and allocated kidney transplants.

On the other hand the pragmatist may question the validity of the outcomes presented. They may request that before moving full steam ahead with transplanting older adults, one is sure that the procedure and subsequent long-term immunosuppression regimes will not shorten their lives. Questions should be raised as to how generalizable the survival outcomes of older adult transplant recipients really are. Given the very small proportion of older adults receiving a transplant, there is a high degree of selection bias. The pragmatist may ask if the improvements in the quality of life of an older adult kidney recipient is worth the increased risk to life in the early post-transplant period? Gill et al. showed that even in low-risk transplant recipients aged >65 years it took 203 days after transplantation with a standard criteria donor kidney for them to reach the same level of survival as their waitlisted dialysis counterparts (291). Though survival after the initial 203 days was much higher in the transplant recipients. Should graft loss in the older adult recipient occur, then mortality is high (292). These points should be made clear to potential recipients to allow for a fair and clear decision making process. The pragmatist will also ask if there are cost benefits to society if we transplant these older adults and question how we identify which older adult will benefit from the procedure.

How will the pragmatist proceed in answering these questions? Randomised clinical trials (RCTs) whereby an older adult with ESRD receives either a kidney transplant or remains on dialysis are neither feasible nor ethical. By the nature of observational studies they are hypothesis generating and therefore cannot prove causation. Furthermore, conventional observational studies examining the outcomes of kidney transplantation

versus dialysis therapy, despite the investigators' best efforts are often plagued by inherent biases; confounding by indication, confounding by contraindication, lag time bias and survival bias to name but a few. However there are methods which could be employed to minimise the effects of selection bias. The most obvious approach is to match the transplant and dialysis groups as closely as possible, another approach could applying a 'pseudo-randomisation' effect such as with an instrumental variable analysis (293).

For now it remains unclear how to determine which older adult is appropriate for kidney transplantation. Most guidelines state that kidney transplantation should not be denied on the basis of age alone, however age related co-morbidities may well be considered as relative contraindications to transplantation (14, 15, 287). With regards to life expectancy, a review by Batabyal et al. found that of the fifteen guidelines reviewed, three stated that the potential recipient should have a minimum of five years life expectancy to be considered a suitable candidate for transplantation (294). One guideline suggested that an anticipated survival of less than two years was an absolute contraindication. However, it is not entirely clear how one should determine life expectancy. Ponticelli et al. recommend that above the standard screens for transplant eligibility older adults should be screened for frailty, co-morbidity and adherence to prescription (295). However there is limited data regarding the impact of frailty (as a marker of physiological reserve) on survival in older adult kidney transplant recipients (16). Though recently Haugen et al. have reported that frailty is independently associated with post-transplantation delirium (odds ratio: 2.05, 95%CI: 1.14; 6.53) (296). Furthermore they reported that recipients with post-transplantation delirium had a 22.4-fold increased risk of discharge to either a nursing facility or rehabilitation centre (296). Even the most widely used co-morbidities scoring system, the Charlson Comorbidity Index fails to consistently predict survival post-transplantation in the older adult (≥70 years) (16). Perhaps for the time being, until we have a clearer idea of which older adults will benefit from kidney transplantation, we may have to rely the physician's instinct?

The older donor

In Chapter 7 we saw that within seven European countries the median age of deceased donors increased from 50 to 55 years over a ten-year period. In the 1990s the median age of a deceased kidney donor in the Eurotransplant region was 36 years and this increased to 54 years in 2016 (20). Whereas in the 1990s deceased donors aged >55 years were considered old and were shunned upon they are now fast becoming the norm. Utilising the older donor kidney allows for (a more) equal access to transplantation. In 1999 the Eurotransplant senior programme (ESP) was established. Within this scheme non-sensitized potential recipients aged >65 years are prioritised for kidneys from deceased donors aged >65

years irrespective of HLA matching (297). Since 2013 Spain has also introduced an old-for-old scheme (17). By longevity matching the donor and recipient the ESP has been successful in increasing the transplantation rates for older adults and reducing the waiting times within the Eurotransplant process for younger adults (297), thereby allowing for a more equal access to transplantation for all age groups.

However, in terms of the philosophical concept of utility, where the allocation of organs is directed to those where the greatest benefit from the organ will be derived, perhaps allocating older donor kidneys to older recipients is not the correct procedure. In Chapter 8 we showed that by ten-year follow-up allocating older donor kidneys to either younger or older recipients led to a six month longer graft survival time in younger recipients than in older recipients. Therefore from a utility perspective, the mathematician could argue that these older donor kidneys should be allocated to younger recipients where the most use from them will be derived. However we clearly demonstrated that young recipients should avoid older donor kidneys. In Chapter 9 we showed that for each one-year increase in the deceased donor age, the ten-year relative risk of patient death for young transplant recipients increased by 2-3%. When we looked at donor quality in terms of the KDRI we saw that for these young transplant recipients every 0.1 increase in the KDRI score was associated with a 7-9% increase in the 10-year relative risk of graft failure.

It is not only the age of deceased kidney donors that has changed over time. In Chapter 7 we reported that between 2005 and 2014 the quality of deceased donor kidneys as measured by the KDRI had decreased. The increase in KDRI, i.e. decrease in kidney quality, was driven not only by increases in donor age, but also by increased numbers of donors with a diagnosis of hypertension and donation after circulatory death. How would the idealist and the pragmatist approach the ethical conundrum of allocating the older/more marginal donor kidney? The idealist may speak of each recipient receiving the best possible kidney available to them. However even the idealist will realise that in the current transplant climate, even the best available kidney at that moment, may not be as good as one hopes it would be. So perhaps the answer lies in rethinking the allocation algorithms. The US has attempted to allocate deceased donor kidneys along the lines of utility by longevity matching the donor kidneys with the lowest KDRI scores to the potential recipients expected to survive the longest (298). Though some have argued that this new allocation system is at the detriment of the potential older or diabetic recipient (299). The KDRI allows one to visualise the quality of a kidney in the light of more factors than just donor age, hypertension and cause of death. Philipse et al., recently showed that by implementing the KDRI score to the decision-making process in a transplant

centre in Antwerp, Belgium, the transplantation rate increased by 5.5% (300). In addition they utilised a greater number of kidneys with a KDRI score <1. A modified version of the KDRI score forms part of the UK allocation system (133). Though not yet adopted by the rest of Europe, this scoring system, or derivatives of it may well be on the European allocation process horizon. Other strategies to maximise the benefits of these marginal donor kidneys include dual transplantation and maximising pre-transplantation conditions such as optimising pre-transplantation organ storage (89).

The pragmatist on the other hand would want to know of parallel outcomes for individuals either receiving a poorer quality kidney or remaining on dialysis. They would question whether it were better to stop with dialysis and receive a poorer quality kidney, or given the inherent risks associated with the first year of transplantation, were it better to remain on dialysis and await a higher quality donor kidney? That is, is it better to receive a small fish or an empty dish? They would also question how long one should hold onto their empty dish for. At what point should one accept a small fish? In other words how long can a young patient remain on dialysis whilst awaiting a younger/better quality kidney before the effects of the waiting time outweigh the benefits of a younger/better quality kidney? To this effect Cohen et al. showed that recipients (aged >40 years) of low-KDRI (<85% KDRI) kidneys from diabetic donors had a 9% lower relative risk of mortality compared with remaining on the waiting-list (301). The pragmatist would encourage further studies along these lines to develop a clear picture of what the outcomes of utilizing older donor kidneys for younger recipients really are. Massie et al. showed that transplantation with high kidney donor profile index kidneys (a derivative of the KDRI), offered a greater survival benefit in recipients aged >50 years compared to those remaining on the waiting-list in hope of a better quality kidney (302). Though their initial (post-transplant) mortality risk was higher, by 5-years of follow-up their cumulative probability of survival was greater than those remaining on the waiting-list in hope of a better quality kidney, even compared to those who eventually received a better quality kidney. It is likely that the greatest beneficiary of these older donor kidneys will remain the older recipient.

The living donor

The first living kidney donor was Madame Renard in 1952; her teenage son Marius Renard, had fallen from a height and lost his only functioning kidney (303). Whilst the initial surgery was a success, he unfortunately died 21 days later from the uraemic effects of graft failure. Living donation has come a long way since this first procedure and whilst the general consensus remains that the long-term risks to the health of the living donor are low, one cannot be sure this will remain the case in light of changing living kidney donor profiles (212).

In Chapter 2 we present the age-, sex- and country-specific lifetime risk estimates for RRT across ten European countries. The most striking findings of this study where the variations in age-specific lifetime risk estimates by both sex and country. The new KDIGO guidelines recommend a personalised risk-based evaluation of potential donors (209). In light of the differences in the lifetime risk of RRT between the US and Europe and indeed between European countries, we recommended that this personalised risk-based assessment considers the country specific estimates. In Chapter 10 we similarly recommend a personalised risk-based assessment to determine the pre-donation risk of hypertensive complications in pregnancy. Whilst no-one would question the need to protect the living donor, in Chapter 10 we reported that the living kidney donor guidelines offer little guidance with regards to post-donation pregnancy in living kidney donors. This is maybe due to the absolute low risk of post-donation pregnancy complications and the low risk of long-term complications from either hypertension in pregnancy or pre-eclampsia. However this could also be due to a lack of available evidence as opposed to a lack of actual effect. Donor nephrectomy is shown to increase post-donation systolic blood pressure by approximately 6 mmHg (95%CI: 2; 11) and diastolic blood pressure by approximately 4 mmHg (95%CI: 1; 7) by ten years follow-up (205). These are undeniably small quantities that can easily be dismissed as clinically irrelevant. However a recent study found that individuals aged 45 to 61 years with a systolic blood pressure of ≥130 mmHg had an increased risk of dementia in later life compared to those with no or low exposure to high systolic blood pressure (HR: 1.29, 95%CI: 1.00; 1.66) (304). The current definition of hypertension includes a systolic blood pressure of 140/90 mmHg. As we learn more about the long-term effects of even a slightly raised blood pressure perhaps we will need to reconsider what are acceptable long-term risks for donors.

Methodological issues

Most of the research presented in this thesis is based on data available in the ERA-EDTA Registry database. This Registry holds over 700,000 patient records with a high level of completeness of the core dataset, it has been operating for over fifty years and covers a substantial portion of Europe (individual patient data from seventeen European countries, all with 100% coverage of the adult population). The size of the Registry database ensures that analyses of rare diseases, even at a subgroup level can be performed and still yield effect estimates with high precision. Furthermore the wide coverage of European countries allows for country comparisons to be drawn. One drawback however is that the ERA-EDTA Registry database describes 'treated' ESRD i.e. those individuals receiving RRT and not those individuals with ESRD receiving conservative therapy. Therefore the true burden of ESRD cannot be determined from this Registry. With

regards to kidney transplantation analysis there are several drawbacks with using registry based data: a transplant is more than its survival potential. The Registry lacks certain transplantation details which would allow for more detailed outcomes, for example episodes of delayed graft function or acute rejection. In addition the lack of certain transplant information such as immunosuppression regimes or pre-implantation biopsy reports means that the outcomes cannot be personalised to individual circumstances. The lack of waiting-list data limits our ability to compare survival outcomes in transplanted individuals with those remaining on dialysis. On the other hand the Registry does have comprehensive follow-up data; should an allograft fail and a transplant recipient returns to dialysis, the ERA-EDTA Registry is more likely to have this data than a transplant registry. Ideally the data from a renal registry should be combined with that of a transplant registry in order to have both comprehensive follow-up data and transplantation data. In four studies included in this theses we were able to merge additional transplantation data from transplant or renal registries. Therefore analysis of various transplantation outcomes with comprehensive follow-up was possible.

The results presented in this thesis arise from observational data. The main limitation of observational data is their inability to prove causality, especially when it comes to the effects of treatments. As discussed earlier in the context of the older recipient, the definitive answer often lies at the end of an RCT. However RCTs are on occasion neither ethical nor feasible. This is particularly the case when comparing the outcomes of a known treatment (for example the gold standard treatment) with one thought likely to be inferior in outcome. In this case comparing the outcomes in young recipients receiving either a low KDRI kidney or a high KDRI kidney. We need to know these RCT outcomes in order to provide a potential recipient with information needed to make an informed decision, but no one would consider such an RCT as ethical. The other problem with performing an RCT is when the outcome of interest is long-term survival. It is not feasible to expect potential dialysis patients to wait at least ten years for the results of an RCT to know what the long-term outcomes of a high KDRI kidney are likely to be.

There is therefore a definite place for observational studies. Though one should always be aware of their limitations. In this thesis the results should be read in the context of likely selection bias. For example in Chapter 6, the older adults aged 75 to 84 years who received a kidney transplant are a very select group of individuals and so their outcomes could not be generalised to all potential older adult transplant recipients. Likewise in Chapter 12 the transplant recipients with a PRD of scleroderma were deemed eligible for transplantation, though we cannot generalise the transplant outcomes to all adults with a

PRD of scleroderma. We have tried to overcome some of the potential selection bias by for example using the paired-analysis approach in Chapter 8 and matching each scleroderma case to ten controls in Chapter 12.

Future research

Transplantation in the 21st century, just like in the previous century is pushing the boundaries of what is acceptable practice within this field. Increased use of higher-risk living donors, higher-risk deceased donor organs and transplants in higher-risk recipients are now far more common. We must keep on top of these changing profiles and be sure that organs are being retrieved from appropriate donors and transplanted into appropriate recipients. In the case of a high-risk potential recipient we should be sure that the potential transplant outcomes outweigh the potential transplant risks. In the case of a deceased donor, the transplantation of a poorer quality organ should not have a detrimental effect on the recipient's survival and in the case of a living donor, the nephrectomy should not have a detrimental effect on the donor's life expectancy or quality of life.

The risks to living donors must remain below an acceptable threshold. There is (rightly) much focus on the long-term risks of death and ESRD amongst donors. However attention should also be placed on the additional effects that a small but premature increase in blood pressure secondary to kidney donation may have on long-term health. We should ensure that the guidance and consent procedure for living kidney donors is improved. One way in which this can be achieved is by increasing the availability of personalised risk scores, only once we know what one's baseline risk is, can we/they determine what an acceptable threshold of additional risk is. These already exist for the long-term risk of ESRD in donors (www.transplantmodels.com/donesrd/), however these were developed and based on US donors. Personalising the long-term risk for donors based on the changing profiles of donors and by country (and where possible by ethnicity) are vital to ensure a potential living kidney donor can make a properly informed decision. The establishment of a European living donor registry should go some way towards answering these questions (289).

Given the shortage of donor kidneys and the variability in transplant outcomes depending on the recipient characteristics it is now more important than ever that we understand which kidney is right for which patient; we must determine which kidney transplant recipients can safely receive poorer quality kidneys, whilst still ensuring a benefit in terms of survival or quality of life in comparison to remaining on dialysis. The questions raised by the pragmatist earlier on in this chapter should be addressed. Kidneys with a high KDRI

are often discarded, potentially wasting a valuable resource. Perhaps by improving the matching of recipient to donor we can also move one step closer to reducing the number of discarded organs. Large sized studies specifically comparing outcomes stratified by age, sex, co-morbidities, and PRD of adults transplanted with higher KDRI kidneys versus remaining on dialysis are needed. These studies should also specify what a 'safe pre-transplantation dialysis duration' is. Perhaps then one will know whether they are better off with a small fish or an empty dish.

Clear guidance for selecting older adults for kidney transplantation is needed. Clearly kidney transplantation is not a suitable procedure for all RRT recipients. However denying a treatment to an individual based on their age alone, whether that process is conscious or unconscious, is not in keeping with a modern, just society. The questions posed by the pragmatist earlier in this chapter regarding the generalisability of the transplant outcomes in this age group should be addressed. With an increasing number of older adult recipients and longer follow-up times it should become more feasible to develop prediction scores in order to identify which older adults would benefit from kidney transplantation, should they want it.

Kidney transplantation is one of the medical success stories of the 20th century and 2019 will see the 65th anniversary of the first successful kidney transplant. Whilst an increasing number of kidney transplant recipients and deceased donors have entered their Golden Years, kidney transplantation may have not yet found its Golden Age.