ORIGINAL ARTICLE

Progressive improvement in short-, medium- and long-term graft survival in kidney transplantation patients in Ireland – a retrospective study

Donal J. Sexton[1], Patrick O'Kelly[1], Yvonne Williams[1,2], William D. Plant[3], Marie Keogan[4], Khairin Khalib[4], Brendan Doyle[5], Anthony Dorman[5], Caner Süsal[6], Christian Unterrainer[6], James Forde[2], Richard Power[2], Gordon Smith[2], Ponnusamy Mohan[2], Mark Denton[1], Colm Magee[1], Declan G. de Freitas[1], Dilly Little[2], Conall M. O'Seaghdha[1] & Peter J. Conlon[1,7]

1 National Kidney Transplant Service, Department of Nephrology and Kidney Transplantation, Beaumont Hospital, Dublin, Ireland
2 Department of Transplant Urology, Beaumont Hospital, Dublin, Ireland
3 The National Renal Office, Health Service Executive of Ireland, Cork University Hospital, University College Cork, Cork, Ireland
4 Department of Immunology, Beaumont Hospital, Dublin, Ireland
5 Department of Pathology, Beaumont Hospital, Dublin, Ireland
6 Collaborative Transplant Study, Institute of Immunology, Heidelberg University, Heidelberg, Germany
7 Royal College of Surgeons in Ireland, Dublin, Ireland

Correspondence
Donal J. Sexton MD, PhD, Department of Nephology and Kidney Transplantation, Beaumont Hospital, Beaumont Road, Dublin 9, Ireland.
Tel.: 01-8093000;
e-mail: dosexton@tcd.ie

SUMMARY

It is often quoted that while short-term graft survival in kidney transplantation has improved in recent years, it has not translated into a commensurate improvement in long-term graft survival. We considered whether this was true of the entire experience of the national kidney transplant program in Ireland. A retrospective analysis of the National Kidney Transplant Service (NKTS) database was undertaken to investigate patient and graft survival for all adult first deceased donor kidney transplant recipients in Ireland, 1971–2015. Three thousand two hundred and sixty recipients were included in this study. Kaplan–Meier methods were used to estimate survival at each time period post transplant for the various eras of transplantation. Uncensored graft survival has improved over the course of the program in Ireland at various time points despite risk factors for graft failure progressively increasing over successive eras. For example the graft survival at 15 years post transplant has increased from 10% in 1971–1975 to 45% by 1996–2000. Ireland has experienced a progressive improvement in long-term graft survival following kidney transplantation. Whether these trends are attributable to biological or nonbiological factors is unclear but likely involves a combination of both.

Transplant International 2019; 32: 974–984

Key words
kidney transplant, long-term, outcomes

Received: 20 October 2018; Revision requested: 23 November 2018; Accepted: 12 June 2019;
Published online: 14 August 2019

Introduction

It is often reported that whilst short-term graft survival in kidney transplantation has improved in recent years it has not translated into a commensurate improvement in long-term graft survival [1–4]. This has been the case in the USA, in particular, but has also been reported in other jurisdictions [5]. We considered whether or not this was true of the National Kidney Transplant Service (NKTS) program in Ireland and set out to review the entire experience of our transplant program with over 5000 kidney transplants spanning 45 years [6].

The national kidney transplant program in Ireland has some attributes, which provide an interesting framework for the investigation of trends in allograft outcomes over time. This service has maintained a

© 2019 Steunstichting ESOT
doi:10.1111/tri.13470

prospective kidney transplant registry with 98.9% complete follow-up in terms of recipient outcome ascertainment. In addition, national healthcare policy in Ireland offers very affordable healthcare for recipients including contemporary immunosuppression medications and access to medical care [7,8]. This may not necessarily be the case in other jurisdictions within Europe or in the US [9–14]. Our objective in this study was to challenge the convention that long-term kidney allograft outcomes are failing to improve by assessing long-term trajectories in Ireland.

Materials and methods

This was a retrospective analysis of the National Kidney Transplant Service (NKTS) Registry [15] to assess allograft and recipient outcomes. We analysed patient and graft survival for all adult (aged ≥ 18 years) first deceased donor kidney transplant recipients in Ireland. Of over 5000 kidney transplants in the Irish program since its inception in 1964, 3260 recipients were first adult deceased donor transplants during the period 1971–2015 and were included in this study. Complete data were available for 98.9% of these recipients included in this study. The NKTS Registry in its entirety is also 98% complete in terms of outcome ascertainment. This is made possible through national mortality and dialysis records, as well as continuous reporting between the 12 nephrology centres nationwide. The NKTS is maintained prospectively and incorporates each new kidney transplant, with coverage back to 1964, and is updated continuously with outcomes such as death and graft failure [6,15].

Kaplan-Meier methods were used to estimate and display survival at each time period post transplant for the various eras of transplantation, which were categorized into 5-year brackets. Multivariable modelling on patient and graft survival outcomes were analysed using Cox Proportional Hazards methods stratified into successive time periods of 5 years with the proportional hazards assumption over time tested using Schoenfeld residuals.

The only component of this study which was directly not based on the NKTS Registry data was the half-life estimates which were solely based on data from the Collaborative Transplant Study (CTS) and provided by the CTS (see Table 4 below).

Changes in maintenance immunosuppression regimes over time in the program are depicted in Fig. 1. All kidney transplant recipients were ABO blood group compatible and had either negative complement dependent cytotoxicity (CDC), flow cross match or virtual cross

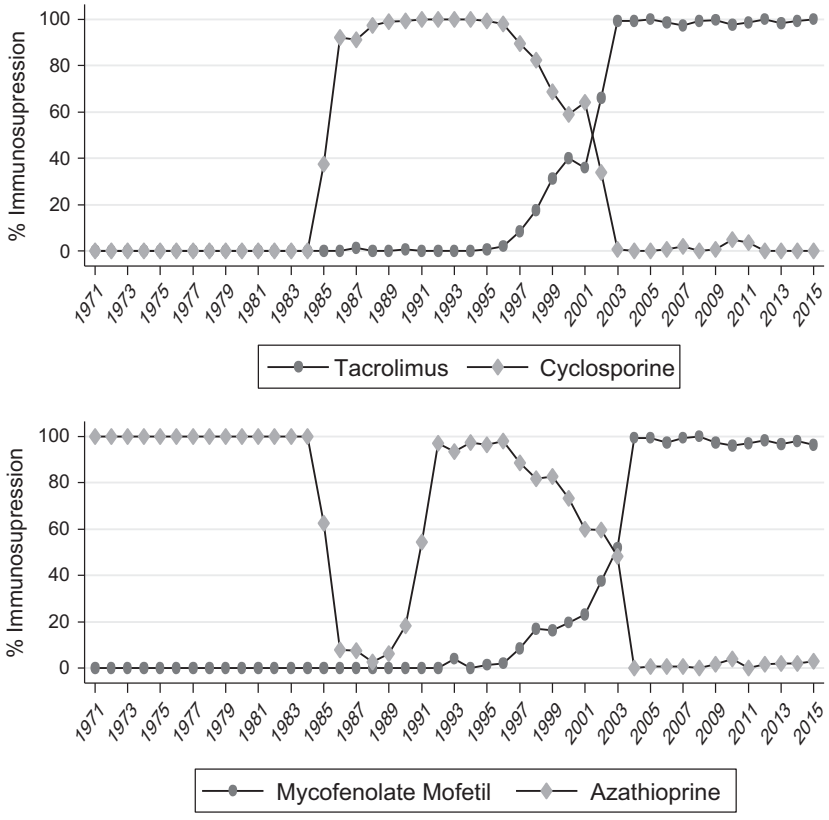

Figure 1 Trends in maintenance immunosuppression over time in the Irish Kidney Transplant Service Program. Trends in induction agents for kidney transplant as a percentage of the total for each period: (a) ATG; 0% from 1971–1985, 0.81% 1986–1990, 4.16% 1991–1995, 3.73% 1996–2000, 1.04% 2001–2005, 0.76% in 2006–2010, 4.01% in 2011–2015. (b) Basiliximab: 1971–2000 0%, 2001–2005 0.21%, 2006–2010 77.1%, 2011–2015 82.66%. (c) No Induction: 1971–1985 100%, 1986–1990 99.19%, 1991–1995 95.84%, 1996–2000 96.27%, 2001–2005 98.75%, 2006–2010 22.14%, 2011–2015 13.32%.

© 2019 Steunstichting ESOT

match assays [6]. The program commenced using flow cytometry routinely in 2004, with high-level screening and DP typing. A and B human leukocyte antigen (HLA) loci were investigated pretransplant in the 1970s and extended to DR loci in the 1980s [6].

Prior to 1986, all recipients were treated with Azathioprine and Prednisolone; thereafter all recipients received Ciclosporin (4 mg/kg BD), Azathioprine (2 mg/kg) and Prednisolone until the introduction of Tacrolimus, Mycophenolate and Prednisolone based regimes circa 2003 because of the summative supportive evidence internationally [6,16–22] (see Fig. 1). Originally, acute rejections were treated with intravenous methylprednisolone and occasionally Muromonab-CD3 (OKT3) was used in resistant cases [6]. Rabbit anti-thymocyte globulin (rATG) has been and still is used as induction therapy for recipients with high immunological risk characteristics and occasionally for steroid-resistant acute rejection. Of the 3260 recipients included in this study, from 1971 to 2015, 71.5% received no induction immunosuppression, 2.18% rATG induction and 26.32% Basiliximab induction. In general the national program does not incorporate desensitization protocols for highly sensitized individuals. While the vast majority of study participants received their kidney transplant at Beaumont Hospital, the very first kidney transplant in Ireland was performed at St Vincent's Hospital, Dublin. Delayed graft function is defined in this study as a requirement for dialysis in the first week following kidney transplant. STATA SE (version 13.1 StataCorp, College Station, TX, USA) was used for the data analysis and graphical presentation.

Half-life estimates of graft and death-censored graft survival provided by CTS

The estimated half-lives and respective 95% confidence intervals were calculated based on available survival information for patients with a minimum of 5-year observation time (if they did not lose their grafts earlier) assuming exponentially distributed survival times [23]. Three thousand two hundred and seventy recipients from Ireland were included based on the following selection criteria: recipients of a first kidney-only deceased donor transplant from 1971 to 2015 and aged $\geq$ 18 years. Recipients from the most recent interval (2011–2015) were not included in the estimations since the 5-year observation criterion was not fulfilled in all cases. These are univariate analyses, which do not consider other changing factors, such as the increasing donor age [23].

Results

Trends in donor and recipient characteristics are displayed in Table 1. Recipient median age (years) increased from 34.5 in 1971–1975 to 52.1 in 2011–2015 and donor median age (years) increased from 20 in 1971–1975 to 48 in 2011–2015, P for trend < 0.001 for both comparisons (Table 1). In terms of anti-HLA panel reactive antibodies (PRA), the proportion of patients in the mid to higher range of PRA increased over time, P for trend < 0.001. The number of HLA mismatches also increased over time from 1.5 in 1976–1980 to 4 in 2011–2015, P for trend < 0.001. Biopsy-proven rejection within the first year (in biopsies performed for clinical indications) decreased over time, from 16.9% in 1971–1975, through a peak of 65.6% in 1981–1985, down to 11.5% in 2011–2015, P for trend < 0.001 (Table 1). Trends in delayed graft function were biphasic with an initial decline and subsequent increase, $P < 0.001$. Cold ischaemic time showed the opposite pattern, $P < 0.001$, but remained low throughout the period. Median time on dialysis prior to transplant (months) rose progressively over time in the program, from 12.8 months in 1971–1975 to 34.4 in 2011–2015, $P < 0.001$ (Table 1).

Patient and uncensored graft survival, expressed as a percentage, is presented in Table 2**.** Uncensored graft and patient survival have improved over the course of the program at various time points (Figs 2a and 3a). For example at 10 years it has increased from 10% in 1971–1975 to 45% by 1996–2000. (Table 2). At 30 years post transplant graft survival, expressed as a percentage, was 4% for allografts transplanted in 1971–1975, 9% for those in 1976–1980 and 15% for those in 1981–1985 (Table 2 and Fig. 3a).

We then further explored early graft and patient survival to investigate whether the improvement in long-term graft function might be explained solely by improvements in early outcomes (Figs 2b and 3b). Life tables to accompany these Kaplan–Meier curves are provided in Table S1. With regard to graft survival, the 2-year survival appeared to progressively improve, however the 5- and 10-year survival appear to have changed more markedly over consecutive eras of transplantation (Table S1). A similar pattern was observed in recipient survival (Fig. 2b and Table S1).

Half-life estimates for graft and death-censored graft survival

CTS half-life estimates indicate a progressive increase in allograft half-life to present (Table 4). Estimated graft

© 2019 Steunstichting ESOT

Table 1. Donor and recipient characteristics in the Irish Kidney Transplant Program over time.

Era	Recipient age (years)Median [IQR]*	Recipient sex % male	Donor age (years) Median [IQR]	Donor sex % male	PRA% 0–10/11–49/50–84/85–100	HLA mismatchNumber (ABDR) Median [IQR]
1971–1975	34.5 [24.2–42.4]	67.5	20 [17–47]	61.4	100/0/0/0	–
1976–1980	39.1 [29.5–46.6]	69	23 [18–38]	61.8	71/18/7/5	1.5 [1–2]
1981–1985	37.3 [27.3–46.4]	69.2	24 [17–42]	63.6	65/18/10/7	2 [2–3]
1986–1990	42.9 [31.3–54.8]	65	30 [19–42]	60.3	69/18/7/6	2 [1–3]
1991–1995	45.1 [32.2–56.0]	65.9	39 [21–51]	62.2	80/11/6/3	3 [2–3]
1996–2000	45.0 [31.9–55.4]	63.6	39 [22–47]	57.2	85/10/4/1	3 [2–4]
2001–2005	47.9 [34.6–58.2]	62.4	41 [25–50]	55.5	89/9/2/1	3 [2–4]
2006–2010	50.0 [37.8–60.1]	62	46 [31–55]	58	58/21/17/4	3 [3–5]
2011–2015	52.1 [39.7–61.8]	63.5	48 [38–55]	58.6	32/34/26/8	4 [3–5]
Trend test sign	Positive	Negative	Positive	Negative	Positive	Positive
Trend test *P* value:	<0.001	0.034	<0.001	0.098	<0.001	<0.001

Era	Deceased donor subtype		Biopsy rejection In year 1 (%)	Delayed Graft function (%)	Cold IschaemiaTime (hours) Median [IQR]	Time on dialysis (months) Median [IQR]
	CAD (%)	DCD (%)				
1971–1975	100	0	16.9	73.9	10 [7–12]	12.8 [6.55–21.1]
1976–1980	100	0	41.9	47.3	10 [8–12]	14.5 [7.85–33.4]
1981–1985	100	0	65.6	30.7	19 [15–22]	16.8 [9.79–33.5]
1986–1990	100	0	35.8	14.2	21 [19–24]	20.2 [8.97–34.1]
1991–1995	100	0	19.5	10	22 [19–25]	16.5 [9.86–27.6]
1996–2000	100	0	26.1	7.4	21 [18–25]	16.1 [9.92–24.9]
2001–2005	100	0	16	16.8	19 [17–22]	20.9 [13.5–32.7]
2006–2010	100	0	12.2	16.2	16 [13–18]	31.3 [19.2–44.5]
2011–2015	94.16	5.84	11.5	17.5	14 [12–17]	34.4 [18.8–51.0]
Trend test sign:	–	–	Negative	Negative	Negative	Positive
Trend test *P* value	–	–	<0.001	<0.001	<0.001	<0.001

PRA, panel reactive antibody; HLA, human leucocyte antigen.

Biopsy rejection in the first year refers to biopsies done for clinical indications rather than protocol biopsies. DCD; kidney donor after cardiac death. CAD; heart beating cadaveric kidney donor.

*Either median and interquartile range [IQR] or percentages are used to compare eras.

© 2019 Steunstichting ESOT

Table 2. Patient and uncensored allograft survival (expressed as a percentage) post kidney transplantation stratified by era over the past 45 years in the Irish Kidney transplant program (*N* = 3260) [see also Figs 2 and 3).

		Year post transplant								
		% Survival								
Era transplanted	Number of recipients	1 %	5 %	10 %	15 %	20 %	25 %	30 %	35 %	40 %
Patient survival										
2011–2015	548	98								
2006–2010	524	99	91							
2001–2005	481	96	90	79						
1996–2000	456	96	87	79	68					
1991–1995	481	94	83	68	54	44				
1986–1990	369	94	83	67	51	39	30			
1981–1985	195	90	78	69	53	44	38	30		
1976–1980	129	73	59	50	40	31	21	19	12	
1971–1975	77	51	39	31	24	17	16	15	13	11
Allograft survival (uncensored)										
2011–2015	548	97								
2006–2010	524	96	88							
2001–2005	481	93	83	67						
1996–2000	456	88	74	58	45					
1991–1995	481	86	69	48	34	26				
1986–1990	369	86	66	44	28	19	13			
1981–1985	195	68	55	44	33	26	21	15		
1976–1980	129	59	46	35	27	19	11	9	7	
1971–1975	77	38	26	17	10	7	5	4	3	3

half-lives increased from 6.7 years during 1971–1975 to 24.9 years during 2001–2005 in the case of graft survival and from 13.4 years to as high as 42.7 years in the case of death-censored graft survival, respectively. (Table 4) There was considerable overlap in half-life 95% confidence intervals.

Discussion

Long-term outcomes following deceased donor kidney transplantation have been progressively improving in Ireland. This contrasts with reports from many other kidney transplant programs internationally, particularly in the USA, which suggest a lack of improvement in long-term outcomes despite effective contemporary immunosuppression [24,25]. These improvements in long-term allograft outcomes have occurred despite an increased representation of features associated with graft failure over time such as increasing donor and recipient age, panel reactivity, HLA mismatches and time on dialysis (Table 1) [26,27]. Although improvements in longer term graft outcomes have also been reported elsewhere, particularly by other European programs and by Australia & New Zealand Dialysis & Transplant Registry (ANZDATA), these reports tend to lack the duration of follow-up we present in this study [5,6,28–30].

A recent CTS study assessed trends in graft failure across 21 countries, and 135 transplant centers in Europe between 1986 and 2015 [31]. This study found an improvement in the hazard of graft failure at 1, 5 and 10 years post transplant over this period. However the authors specify that while the improvements in the first 5 years post transplant have decreased since the year 2000, improvements after 5 years did not appear to plateau [31]. As a result, the improvements in long-term function were greater than short-term improvements from 2000 to 2015 [31]. This study provides good evidence of generalized improvements across the European region as a whole gleaned from a larger diverse composite cohort. However, the inherent heterogeneity between different sites makes the interpretation of these findings for individual programs more difficult to discern. This may be particularly true for comparisons to the early eras. It is also possible that data from larger EU countries are dominating the contribution to the overall estimates. Because the kidney transplant program in Ireland is based out of a single unit, perhaps these data

© 2019 Steunstichting ESOT

may provide a more homogenous substrate for comparisons of outcomes over different time periods, particularly for comparisons to very early eras. In addition, with a single site forming the basis of the national kidney transplant program in Ireland it is perhaps easier to infer the possible impacts of changes to policy and practice over time. However, this may also limit the generalizability of our findings to other programs.

Factors which associated with graft failure from multivariable models in the Irish program included older era of transplant, increasing donor age, donor sex and cold ischaemia time (Table 3). These findings were consistent with the larger CTS study across Europe [31]. Half-life estimations of graft survival performed by CTS, based on observed death-censored graft failure rates in Ireland, also indicated continued improvement in long-term graft survival (Table 4).

Improvements in early graft outcomes have been consistently reported across multiple territories, with comparable 1-year allograft survival rates between Europe and the USA, because of factors such as the reduction in hyperactive rejection resulting from improved immunological characterisation [5,32]. Intermediate outcomes are also improving, even in the USA, with a

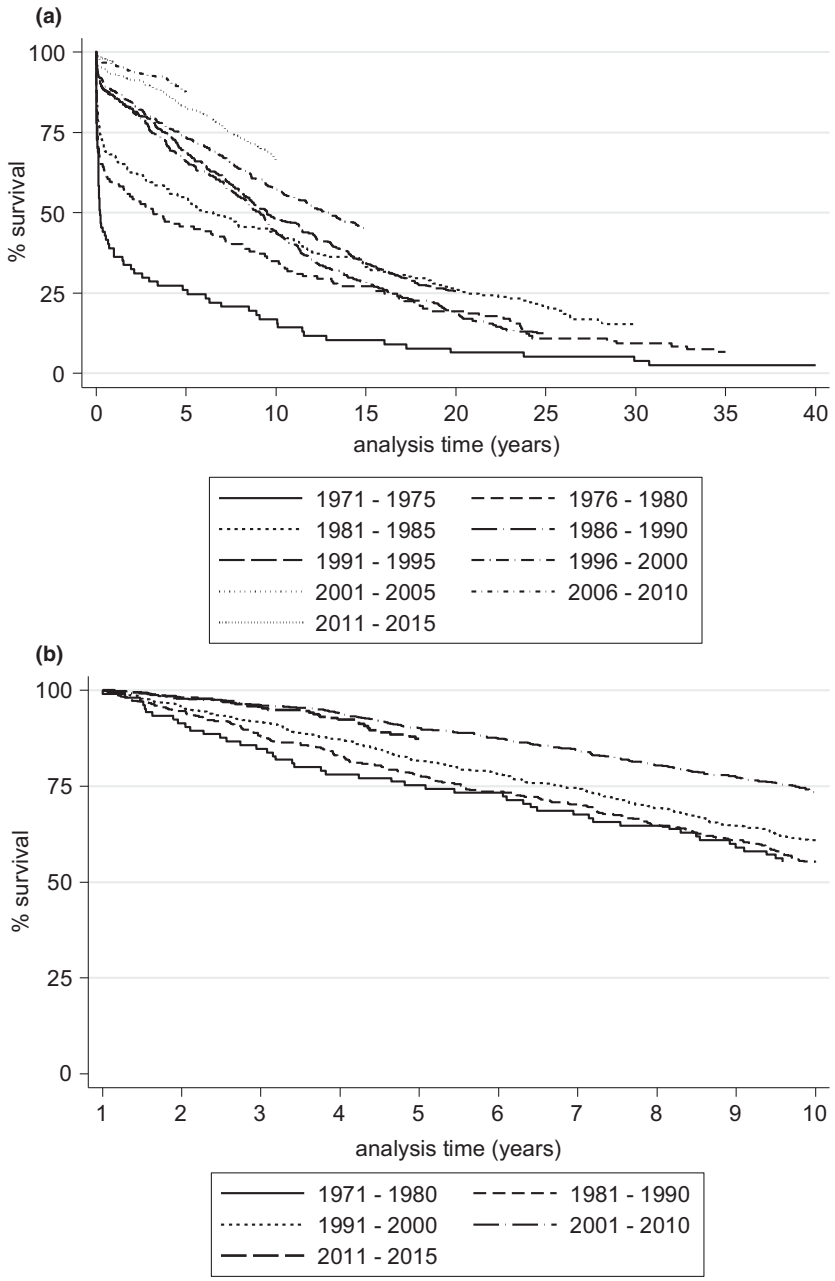

Figure 2 (a) Patient (recipient) survival over the course of the National Kidney Transplant Service Program in Ireland stratified by era of transplant (N = 3260). (b) Patient survival by era of transplantation conditional on survival in the first year following kidney transplant (N = 3260).

© 2019 Steunstichting ESOT

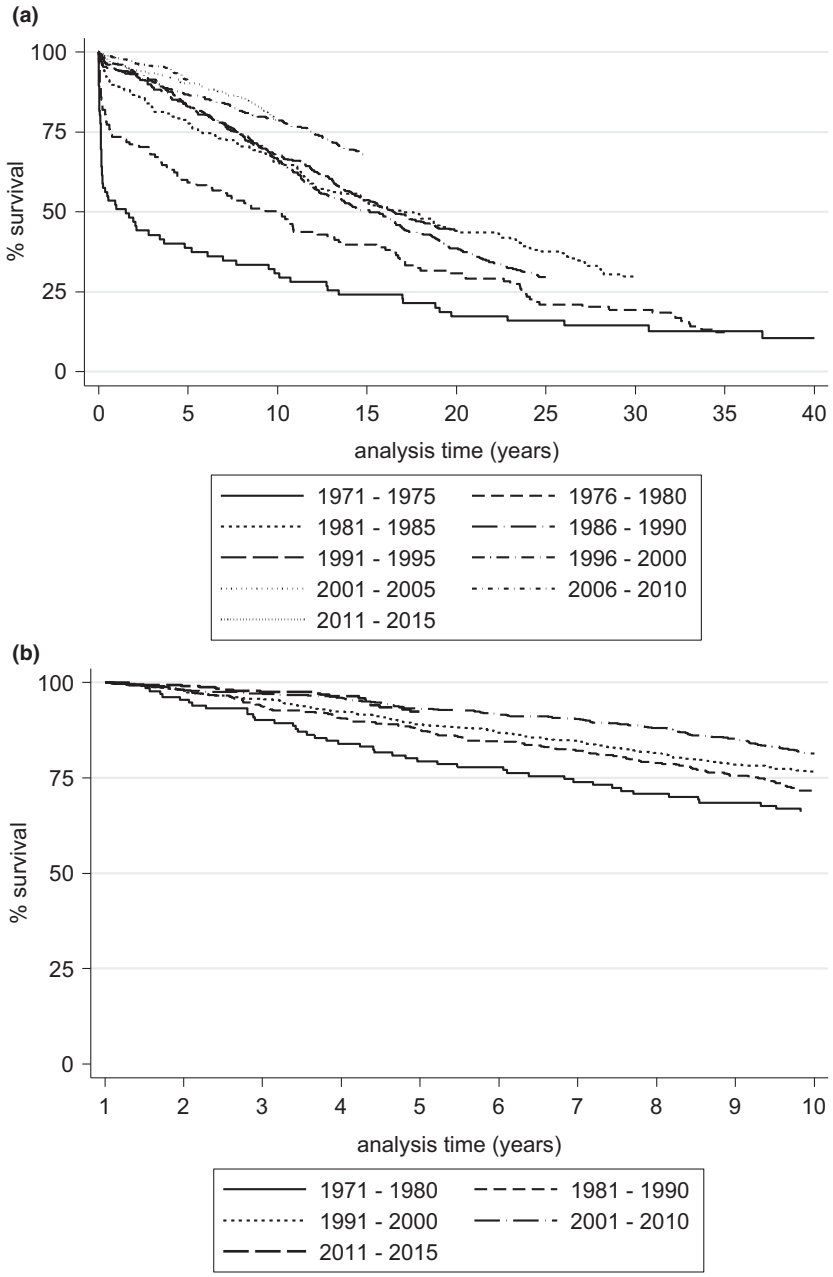

Figure 3 (a) Graft survival (uncensored) over the course of the National Kidney Transplant Program in Ireland stratified by era of transplant (*N* = 3260). (b) Graft survival by era of transplantation conditional on survival in the first year following kidney transplant (*N* = 3260).

reduction in graft failure over the first 3 years despite increasingly deleterious risk factors for graft failure, coincident with the pervasive use of Tacrolimus and Mycophenolate based regimes [3]. However, Lamb *et al*. [2] assessed changes in graft survival in the USA from 1989 to 2005, and found that, while attrition rates beyond the first year did show small improvements, the largest change was in first year attrition rates. Improved long-term allograft survival may be partly attributable to these improvements in the early graft survival, but, as pointed out by Gaston, emerging data challenges the concept that early events are predominantly responsible for late graft failures [33]. Our analysis suggests that while there has been a progressive improvement in short-term outcomes (Figs 2b and 3b), this does not appear to solely explain the long-term improvements.

These improvements in short-term outcomes over the past several decades in the USA do not appear to have translated into comparable improvements in long-term outcomes [4]. Deciphering the hierarchical importance of donor and recipient biologic and socioeconomic factors or medical treatment responsible for this discrepancy is difficult. Wang *et al*. [4] suggest that differences in case mix, allocation policy and healthcare

© 2019 Steunstichting ESOT

Table 3. Multivariable models for risk factors associated with recipient and graft survival over follow up.

	Recipient survival			Graft survival (uncensored)		
Variable	AHR	95% CI	*P* value	AHR	95% CI	*P* value
Era*	0.790	0.749, 0.833	<0.001	0.730	0.701, 0.760	<0.001
Recipient age						
Reference age						
45–54	1.000	–	–	1.000	–	–
18–34	0.149	0.115, 0.193	<0.001	0.840	0.709, 0.996	0.045
35–44	0.451	0.358, 0.569	<0.001	0.807	0.669, 0.974	0.026
55–64	1.699	1.399, 2.063	<0.001	0.979	0.819, 1.169	0.814
65–77	2.553	1.991, 3.274	<0.001	1.044	0.833, 1.309	0.707
Male sex	1.191	1.022, 1.388	0.025	0.949	0.839, 1.074	0.406
Donor age						
Reference age						
19–29	1.000	–	–	1.000	–	–
<18	1.076	0.831, 1.393	0.577	1.135	0.927, 1.389	0.222
30–39	1.059	0.810, 1.383	0.675	0.971	0.783, 1.195	0.779
40–49	1.162	0.922, 1.464	0.205	1.145	0.954, 1.375	0.145
50–59	1.135	0.896, 1.437	0.294	1.238	1.023, 1.498	0.028
60–74	1.188	0.847, 1.669	0.318	1.183	0.876, 1.598	0.272
Donor sex	0.993	0.859, 1.149	0.930	0.853	0.755, 0.962	0.010
PRA group	0.932	0.848, 1.024	0.141	0.988	0.910, 1.073	0.776
Number HLA mismatch	1.023	0.965, 1.085	0.444	1.033	0.986, 1.083	0.173
Cold ischaemic time	1.012	0.999, 1.024	0.072	1.017	1.007, 1.028	0.001
Time on dialysis	1.003	1.001, 1.005	0.002	1.001	0.998, 1.004	0.452

AHR; adjusted hazard ratio, CI; confidence interval, *P*; *P* value.

The unit of measure for each variable of interest above included: cold ischaemic time in hours and time on dialysis in months. PRA was grouped into the following categories grouped by 0–10%, 11–49%, 50–84%, 85–100% and male sex was used as the reference within donor sex.

*Eras in 10 year periods commencing in 1971 except the last era which was a 5-year period, 2011–2015.

Table 4. Half-life estimates and corresponding 95% confidence intervals (CI) of graft and death-censored graft survival of adult first deceased donor kidney-only transplants.

		Graft survival		Death-censored graft survival	
Transplant years	Patients	Half-life	95% CI	Half-life	95% CI
1971–1975	80	6.7	3.6–12.5	13.4	5.6–32.3
1976–1980	127	11.0	6.8–17.7	13.4	7.9–22.6
1981–1985	194	12.5	8.5–18.4	19.1	11.9–30.7
1986–1990	369	10.7	8.5–13.5	18.6	13.8–25.2
1991–1995	481	12.9	10.3–16.0	21.3	16.1–28.1
1996–2000	460	15.3	12.0–19.5	26.6	19.4–36.5
2001–2005*	486	24.9	18.8–33.0	42.7	29.5–61.8

*The graft half-life for 2001–2005 is projected rather than observed.

insurance coverage may partially explain this lack of improvement in long-term function. Recent reports also suggest that long-term graft outcomes in Australia, New Zealand and the United Kingdom, exceed those of the USA, [34] and each country apart from the US have universal health insurance coverage and medication availability [30,34–39]. Other reports from Europe suggest that while long-term outcomes appear to be improving, the gains in short-term outcomes may have plateaued [31].

© 2019 Steunstichting ESOT

Undoubtedly the improvements in long-term outcomes in Ireland compared to jurisdictions such as the US could potentially represent a selection bias, with a more racially, genetically and immunologically heterogeneous donor and recipient profile elsewhere [3,40,41]. However, the increased risk of adverse outcomes such as transplant rejection and graft loss known to associate with black race/ethnicity in the USA may not translate to other jurisdictions such as the United Kingdom, perhaps further evidence for the importance of nonbiological factors [42].

Since the Irish kidney transplant program has almost 100% recipient follow-up and National healthcare policy in Ireland removes some of the health inequalities associated with race and socioeconomic status seen in other programs, it provides an interesting substrate for assessing trends in allograft survival resulting from contemporary clinical management [43,44]. In addition, although there is no direct evidence of superior medication compliance amongst Irish transplant recipients, failure to attend transplant clinic appointments is known to be relatively rare amongst recipients in Ireland [6,43,45].

Evidence exists that socioeconomic factors such as access to medical care in other countries contributes to poorer outcomes following kidney transplant [41,46]. As of 2013 Medicare coverage for most kidney transplant recipients in the US lasted only 3 years, which exposed transplant recipients to the expense of funding their immunosuppressive medications [47]. This report estimated that 40 000 recipients in the US were at risk for cost-related nonadherence [44].

Factors in addition to advances in immunosuppression protocols have likely contributed to improved long-term outcomes such as the developments in immunological assessments for donor specific antibodies and transplant glomerulopathy, the management of cardiovascular disease, cancer and opportunistic infections following transplantation, improved characterization of the BK virus and perhaps improvements in the treatment of primary diseases such as glomerulonephritis subtypes [48,49]. Our group has also previously published on the influence of flow cytometry cross matching on improved graft outcomes [50]. Other possible explanations for the discrepancy in findings between Ireland and other programs include: the possibility of lower deceased donor quality elsewhere, or a lower rate of transplantation in Ireland overall in comparison to regions such as the US.

With regard to patient survival, the gradual improvement in recipient survival seen in this study is commensurated with improvements seen in the general population and the dialysis population over a similar time frame [51]. These improvements in patient and graft survival have been mirrored by an improved survival in the general population, for instance, life expectancy has increased on average by 6.1 years for men and 4.9 years for women over the last 20 years in Ireland [52]. Improvements in graft survival in this setting is perhaps more impressive since a reduction in graft failure rates appears to have occurred despite an inflation in the population at risk. An additional analysis assessing patient and graft survival from dialysis initiation may be of merit.

Limitations of this study include its retrospective nature and since the projections for graft survival provided are speculative simulations; the lower failure rates in recent years may elevate the error around the model projections. In addition, since the projections are based on observed trends in graft failure rates, they may assume a constant rate of improvement in graft survival rather than a plateau effect being reached at certain stages. However, it ought to be acknowledged that a number of the 95% confidence intervals for projected graft survival overlap (Table 4), and it is uncertain at this point internationally whether these long-term improvements will indeed plateau or continue [31].

Whilst acknowledging systematic heterogeneity amongst the various kidney transplantation programs worldwide, and being cognizant of the need to continue to improve transplant care, [53] it is no longer true to suggest that long-term outcomes in kidney transplantation are failing to improve. The reasons for this improvement are unclear but likely represent a combination of biological and nonbiological factors.

Authorship

DJS, POK, PJC: Study design and concept. POK: Data Analysis and creation of graphs. DJS, POK, YW, WDP, MK, KK, BD, AD, CS, CU, JF, RP, GS, PM, MD, CM, DdF, DL, CM, PJC: Interpretation of results. POK, YW: Data management and retrieval. DJS, POK, YW, WDP, MK, KK, BD, AD, CS, CU, JF, RP, GS, PM, MD, CM, DdF, DL, CM, PJC: Drafting of manuscript and critical editing.

Funding

The authors have declared no funding.

Conflicts of interest

The authors have declared no conflicts of interest.

© 2019 Steunstichting ESOT

Acknowledgements

We would also like to acknowledge all nephrologists as well as previous kidney transplant surgeons working in Ireland who have cared for kidney transplant recipients to date. This work was presented as a moderated poster at the *British Transplant Society* annual conference 2018 and judged to be best in category.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. To accompany Fig. b for patient survival and Fig. b for uncensored graft survival in the first 10 years stratified by transplant era ($N = 3260$).

REFERENCES

1. Meier-Kriesche HU, Schold JD, Srinivas TR, Kaplan B. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. *Am J Transplant* 2004; **4**: 378.
2. Lamb KE, Lodhi S, Meier-Kriesche HU. Long-term renal allograft survival in the United States: a critical reappraisal. *Am J Transplant* 2011; **11**: 450.
3. Keith DS, Vranic G, Nishio-Lucar A. Graft function and intermediate-term outcomes of kidney transplants improved in the last decade: analysis of the United States Kidney Transplant Database. *Transplant Direct* 2017; **3**: e166.
4. Wang JH, Skeans MA, Israni AK. Current status of kidney transplant outcomes: dying to survive. *Adv Chronic Kidney Dis* 2016; **23**: 281.
5. Gondos A, Dohler B, Brenner H, Opelz G. Kidney graft survival in Europe and the United States: strikingly different long-term outcomes. *Transplantation* 2013; **95**: 267.
6. Traynor C, Jenkinson A, Williams Y, *et al.* Twenty-year survivors of kidney transplantation. *Am J Transplant* 2012; **12**: 3289.
7. https://www.hse.ie/eng/staff/pcrs/about-pcrs/.
8. https://www.hse.ie/eng/services/list/1/schemes/drugspaymentscheme/.
9. Searles A, Doran E, Faunce TA, Henry D. The affordability of prescription medicines in Australia: are copayments and safety net thresholds too high? *Aust Health Rev* 2013; **37**: 32.
10. Morgan S, Kennedy J. Prescription drug accessibility and affordability in the United States and abroad. *Issue Brief (Commonw Fund)* 2010; **89**: 1.
11. Zaprutko T, Kopciuch D, Kus K, *et al.* Affordability of medicines in the European Union. *PLoS ONE* 2017; **12**: e0172753.
12. Gordon EJ, Prohaska TR, Sehgal AR. The financial impact of immunosuppressant expenses on new kidney transplant recipients. *Clin Transplant* 2008; **22**: 738.
13. James A, Mannon RB. The cost of transplant immunosuppressant therapy: Is this sustainable? *Curr Transplant Rep* 2015; **2**: 113.
14. Muduma GTA, Dam S, Hawken N, Aballea S, Odeyemi I. Conference proceeding: International Society for Pharmacoeconomics and Outcomes "The Economic Burden after Renal Transplantation in Europe. *Presented at the ISPOR 21st Annual International Meeting, 21–25 May 2016, Washington, DC, USA*. 2016. Available at: https://wwwispororg/research_pdfs/52/pdffiles/PUK16pdf
15. National Renal Transplant Registry. Available at: https://wwwhiqaie/areas-we-work/health-information/data-collections/national-renal-transplant-registry.
16. Johnson C, Ahsan N, Gonwa T, *et al.* Randomized trial of tacrolimus (Prograf) in combination with azathioprine or mycophenolate mofetil versus cyclosporine (Neoral) with mycophenolate mofetil after cadaveric kidney transplantation. *Transplantation* 2000; **69**: 834.
17. Margreiter R, European Tacrolimus vs Ciclosporin Microemulsion Renal Transplantation Study Group. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicentre study. *Lancet* 2002; **359**: 741.
18. Gonwa T, Johnson C, Ahsan N, *et al.* Randomized trial of tacrolimus + mycophenolate mofetil or azathioprine versus cyclosporine + mycophenolate mofetil after cadaveric kidney transplantation: results at three years. *Transplantation* 2003; **75**: 2048.
19. Ahsan N, Johnson C, Gonwa T, *et al.* Randomized trial of tacrolimus plus mycophenolate mofetil or azathioprine versus cyclosporine oral solution (modified) plus mycophenolate mofetil after cadaveric kidney transplantation: results at 2 years. *Transplantation* 2001; **72**: 245.
20. Halloran P, Mathew T, Tomlanovich S, Groth C, Hooftman L, Barker C. Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. The International Mycophenolate Mofetil Renal Transplant Study Groups. *Transplantation* 1997; **63**: 39.
21. Miller J, Mendez R, Pirsch JD, Jensik SC. Safety and efficacy of tacrolimus in combination with mycophenolate mofetil (MMF) in cadaveric renal transplant recipients. FK506/MMF Dose-Ranging Kidney Transplant Study Group. *Transplantation* 2000; **69**: 875.
22. Bannon FJ, McCaughan JA, Traynor C, *et al.* Surveillance of nonmelanoma skin cancer incidence rates in kidney transplant recipients in Ireland. *Transplantation* 2014; **98**: 646.
23. Collett D. *Modelling Survival Data in Medical Research*. London: Chapman & Hall, 1994: 116–119.
24. Ekberg H, Tedesco-Silva H, Demirbas A, *et al.* Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med* 2007; **357**: 2562.
25. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009; **9**(Suppl 3): S1.
26. Stegall MD, Gaston RS, Cosio FG, Matas A. Through a glass darkly: seeking clarity in preventing late kidney transplant failure. *J Am Soc Nephrol* 2015; **26**: 20.
27. Gaston RS, Fieberg A, Hunsicker L, *et al.* Late graft failure after kidney transplantation as the consequence of late versus early events. *Am J Transplant* 2017.
28. Galichon P, Xu-Dubois YC, Finianos S, Hertig A, Rondeau E. Clinical and

© 2019 Steunstichting ESOT

histological predictors of long-term kidney graft survival. *Nephrol Dial Transplant* 2013; **28**: 1362.
29. Johnston O, O'Kelly P, Spencer S, *et al*. Reduced graft function (with or without dialysis) vs immediate graft function–a comparison of long-term renal allograft survival. *Nephrol Dial Transplant* 2006; **21**: 2270.
30. http://www.anzdata.org.au/anzdata/AnzdataReport/40thReport/c07_transplant_2016_v1.0_20180509.pdf.
31. Coemans M, Susal C, Dohler B, *et al*. Analyses of the short- and long-term graft survival after kidney transplantation in Europe between 1986 and 2015. *Kidney Int* 2018.
32. Phelan PJ, O'Kelly P, Tarazi M, *et al*. Renal allograft loss in the first post-operative month: causes and consequences. *Clin Transplant* 2012; **26**: 544.
33. Gaston RS. Improving long-term outcomes in kidney transplantation: towards a new paradigm of post-transplant care in the United States. *Trans Am Clin Climatol Assoc* 2016; **127**: 350.
34. Merion RM, Goodrich NP, Johnson RJ, *et al*. Kidney transplant graft outcomes in 379 257 recipients on 3 continents. *Am J Transplant* 2018; **18**: 1914.
35. USRDS Annual Data Report 2017. Available at: https://wwwusrdsorg/2017/download/v2_c06_Transplant_17pdf.
36. Hart A, Smith JM, Skeans MA, *et al*. OPTN/SRTR 2016 annual data report: kidney. *Am J Transplant* 2018; **18** (Suppl 1): 18.
37. http://atcmeetingabstracts.com/abstract/comparison-of-20-year-patient-and-graft-survival-for-all-types-of-solid-organ-transplants-txs/.
38. European Renal Association Annual Report. https://wwwera-edta-regorg/files/annualreports/pdf/AnnRep2015pdf.
39. NHSBT Annual Report. https://www.odt.nhs.uk/statistics-and-reports/organ-specific-reports/.
40. Kerman RH, Kimball PM, Van Buren CT, Lewis RM, Kahan BD. Possible contribution of pretransplant immune responder status to renal allograft survival differences of black versus white recipients. *Transplantation* 1991; **51**: 338.
41. Gordon EJ, Ladner DP, Caicedo JC, Franklin J. Disparities in kidney transplant outcomes: a review. *Semin Nephrol* 2010; **30**: 81.
42. Tahir S, Gillott H, Jackson-Spence F, *et al*. Do outcomes after kidney transplantation differ for black patients in England versus New York State? A comparative, population-cohort analysis. *BMJ Open* 2017; **7**: e014069.
43. Ward FL, O'Kelly P, Donohue F, *et al*. The influence of socioeconomic status on patient survival on chronic dialysis. *Hemodial Int* 2015; **19**: 601.
44. Potter LM, Maldonado AQ, Lentine KL, *et al*. Transplant recipients are vulnerable to coverage denial under Medicare Part D. *Am J Transplant* 2018.
45. https://www.hse.ie/eng/.
46. Eckhoff DE, Young CJ, Gaston RS, *et al*. Racial disparities in renal allograft survival: a public health issue? *J Am Coll Surg* 2007; **204**: 894; discussion -3.
47. Tanriover B, Stone PW, Mohan S, Cohen DJ, Gaston RS. Future of Medicare immunosuppressive drug coverage for kidney transplant recipients in the United States. *Clin J Am Soc Nephrol* 2013; **8**: 1258.
48. Lefaucheur C, Loupy A, Zeevi A. Complement-binding anti-HLA antibodies and kidney transplantation. *N Engl J Med* 2014; **370**: 85.
49. Pippias M, Stel VS, Areste-Fosalba N, *et al*. Long-term kidney transplant outcomes in primary glomerulonephritis: analysis from the ERA-EDTA registry. *Transplantation* 2016; **100**: 1955.
50. Limaye S, O'Kelly P, Harmon G, *et al*. Improved graft survival in highly sensitized patients undergoing renal transplantation after the introduction of a clinically validated flow cytometry crossmatch. *Transplantation* 2009; **87**: 1052.
51. Foster BJ, Mitsnefes MM, Dahhou M, Zhang X, Laskin BL. Changes in excess mortality from end stage renal disease in the United States from 1995 to 2013. *Clin J Am Soc Nephrol* 2018; **13**: 91.
52. https://www.cso.ie/en/index.html.
53. Halloran PF, Famulski KS, Reeve J. Molecular assessment of disease states in kidney transplant biopsy samples. *Nat Rev Nephrol* 2016; **12**: 534.

© 2019 Steunstichting ESOT