UNIVERSITEIT GENT

Retransplantation after a (failed) living related transplant

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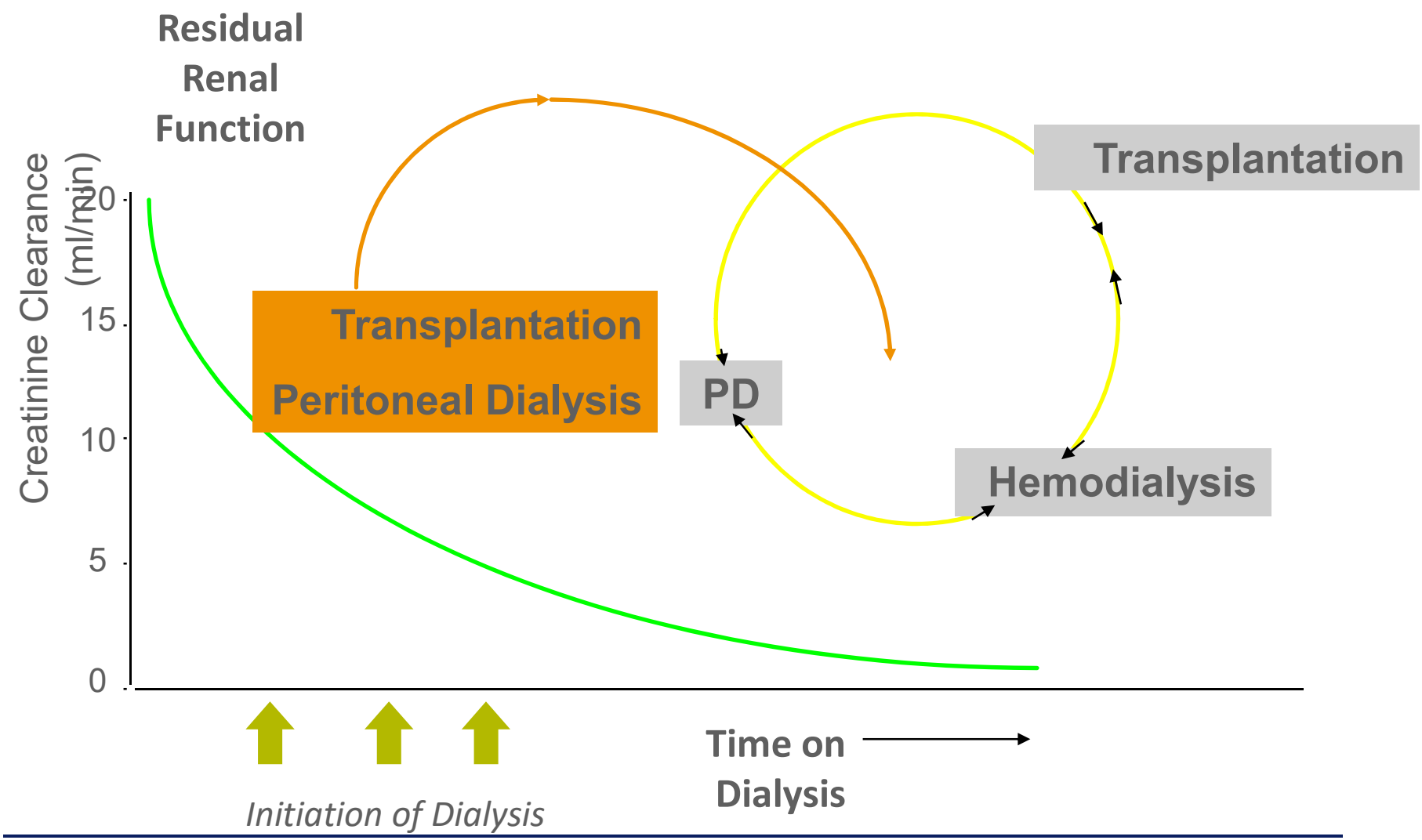
Integrated ESRD Care



Patient survival 1st graft

TABLE 3. OUTCOME AMONG RECIPIENTS OF FIRST CADAVERIC TRANSPLANTS, ACCORDING TO CHARACTERISTICS AT THE TIME OF INITIAL PLACEMENT ON THE WAITING LIST, 1991–1997.*

GROUP	RELATIVE RISK 18 MO AFTER TRANSPLANTATION (95% CI)†	P VALUE	TIME AT WHICH RISK OF DEATH EQUALS THAT IN REFERENCE GROUP	TIME AT WHICH LIKELIHOOD OF SURVIVAL EQUALS THAT IN REFERENCE GROUP	PROJECTED YEARS OF LIFE (IN REFERENCE GROUP) WITHOUT TRANSPLANTATION†‡	PROJECTED YEARS OF LIFE WITH TRANSPLANTATION‡
			days after transplantation			
All recipients of first cadaveric transplants	0.32 (0.30–0.35)	<0.001	106	244	10	20
Age						
0–19 yr	0.33 (0.12–0.87)	0.03	3	5	26	39
20–39 yr	0.24 (0.20–0.29)	<0.001	11	57	14	31
40–59 yr	0.33 (0.29–0.37)	<0.001	95	251	11	22
60–74 yr	0.39 (0.33–0.47)	<0.001	148	369	6	10
Sex						
Male	0.34 (0.30–0.38)	<0.001	110	255	10	19
Female	0.30 (0.26–0.34)	<0.001	94	220	11	23

Wolfe NEJM 1999

Retransplanting a previously transplanted kidney

Retransplanting a previously transplanted kidney

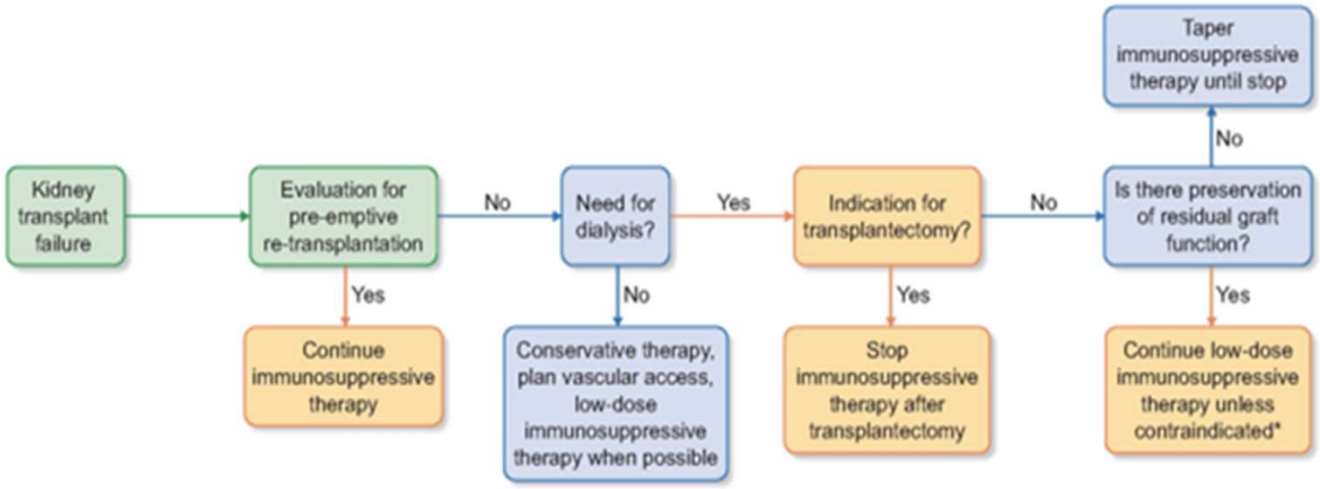
Karakizlis Clin Transplant 2022, 36/3

- ET database 1995-2015 : 9 out of 68554 allocated kidneys
- Mean 1st serum creatinine 1 mg/dl and 2nd S creatinine 1,4 mg/dl
- Mean graft survival 1st graft 50 months (2-110m)

Retransplantation : solid organ transplantation after kidney transplantation

Retransplanting a previously transplanted patient

FIGURE 1 Suggested algorithm for the management of immunosuppressive therapy after kidney transplant ...



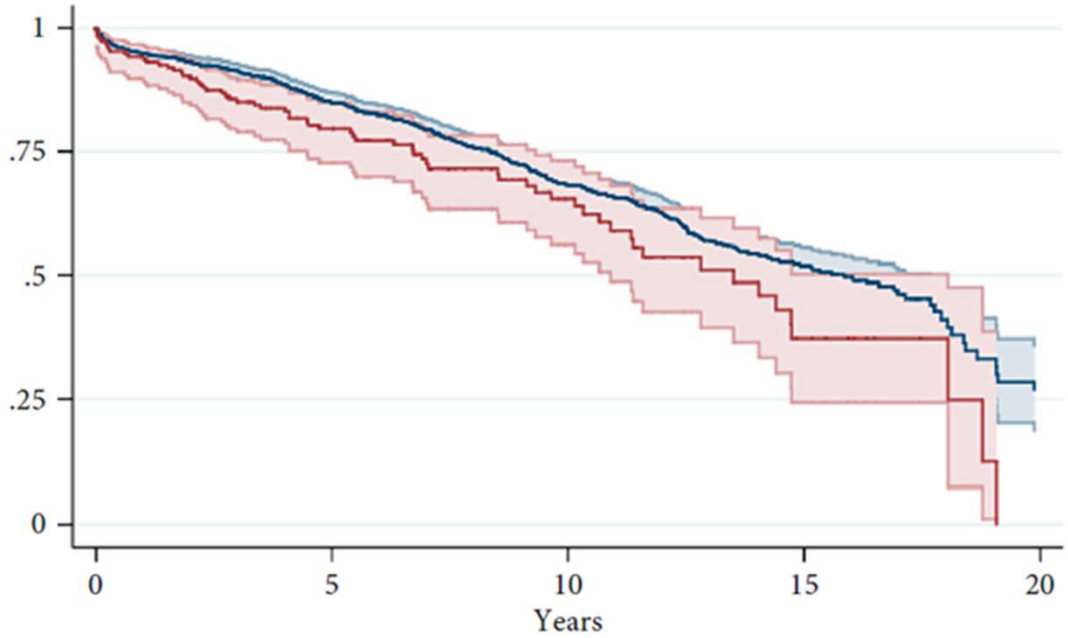
CKJ 2021, 13, 98-106

Listing for transplantation

	2nd transplantation
n	283
Relisted and retransplanted	192 (67.8%)
On waiting list	22 (7.8%)
Death on waiting list	2 (0.7%)
Removed from list	1 (0.4%)
Patient moved to another country	1 (0.4%)
Death while evaluation for wait-listing	6 (2.1%)
Excluded from retransplantation due to reduced general condition	24 (8.5%)
Malignancy	5 (1.8%)
Infection	3 (1.1%)
Increased risk for rejection	2 (0.7%
Compliance problems	3 (1.1%)
Unknown	6 (2.3%)
Patient refused relisting	15 (5.3%)

Ehrsam J Transplant 2022

Death-censored graft survival



Kaplan-Meier curve for death-censored graft survival:

	time from kidney transplantation (years)				
	0	5	10	15	20
1st transplantation (blue)	1333	893	460	139	16
2nd transplantation (red)	189	110	51	13	0

Risk factors for graft loss in 1st and 2nd KTx

	HR	95% CI	*p* value
Number of transplantations			
1	Ref		
2	1.5	1.1–2.0	0.003
≥3	3.3	1.7–6.1	<0.001
Recipient age (years)			
<50	Ref		
50–59	1.2	0.9–1.6	0.1
60–69	1.9	1.4–2.5	<0.001
≥70	2.9	1.8–4.8	<0.001
Time on dialysis (years)			
<1	Ref		
1-2	1.2	0.9–1.5	0.2
2–4	1.4	1.1–1.8	0.003
>4	1.7	1.3–2.2	<0.001
Charlson–Deyo index*			
2 (kidney disease only)	Ref		
3 (≤1 mild comorbidity)	1.2	0.9–1.6	0.1
4 (≥2 mild or 1 moderate comorbidity)	1.8	1.4–2.4	<0.001
≥5 (multiple comorbidities)	2.3	1.7–3.0	<0.001
Smoking	1.3	1.1–1.5	0.01
Comorbidities*			
Myocardial infarction	1.3	1.0–1.7	0.04
Congestive heart failure	3.1	2.1–4.5	<0.001
PAD	1.4	1.0–1.8	0.03
Diabetes with end organ failure	1.2	1.0–1.3	0.02
Moderate – severe liver disease	1.3	1.0–1.6	0.04

Likelihood of retransplantation

	LR	95% CI	*p* value
Age < 65 years at graft loss	2.7	1.3–5.5	0.008
≤1 light comorbidity (Charlson–Deyo index ≤ 3)	1.5	1.0–2.4	0.04
BMI < 30 kg/m^2	2.1	1.0–4.8	0.04
Previous graft survival > 5 years	1.5	1.1–2.0	0.01
Prior dialysis < 3 years	1.5	1.2–2.4	0.001
Initial peritoneal dialysis	1.5	1.1–2.2	0.02
Number of previous transplantations	1.4	1.0–2.0	0.04

Risk factors for graft loss in retransplant

	HR	95% CI	*p* value
Age ≥ 50 years at retransplantation	1.8	1.1–2.9	0.03
≥1 light comorbidity (Charlson–Deyo index ≥ 3)	1.8	1.1–3.0	0.03
Clavien–Dindo index ≥ IV after first transplantation	2.9	1.1–7.5	0.03
Previous graft survival < 2 years	1.6	1.0–2.6	0.04
Prior dialysis ≥ 1 year	1.7	1.0–3.2	0.04
Current smoker	2.6	1.6–4.5	<0.001

Note. HR, hazard ratio; CI, confidence interval.

Factors to be considered for repeated KTx

Near or after allograft failure

Management of chronic kidney disease and comorbidity

Anemia, mineral and bone disorder, residual kidney function, dialysis access, nutrition and frailty, hypertension, diabetes, dyslipidemia

Assessment of preemptive kidney retransplantation

Timely relisting, living donor, deceased-donor organ allocation priority (eg, pediatrics)

Immunosuppression management

Low-dose maintenance vs weaning, sensitization risk, cardiovascular risk, infectious risk, malignancy risk, medication side effect

Failed transplant nephrectomy

Indication and timing, surgical risk, surgical technique (subcapsular vs extracapsular), immunological risk, chronic inflammation

During retransplant workup

Standard workup for kidney transplant candidates

Including cardiovascular risk assessment

Immunological risk assessment

High-resolution HLA typing, anti-HLA antibody profile, non-HLA antibody screening when indicated, HLA typing of prior donor(s)—repeat mismatch, acceptable and unacceptable antigens

Recurrent disease risk assessment

Immunoglobulin A nephropathy, focal and segmental glomerulosclerosis, membranoproliferative glomerulonephritis, membranous nephropathy, anti-neutrophil cytoplasmic antibody-associated glomerulonephritis, antiglomerular basement membrane disease, fibrillary glomerulonephritis, systemic lupus erythematosis, atypical hemolytic uremic syndrome, Schoenlein-Henoch purpura, primary hyperoxaluria

Thrombosis risk assessment

Primary and secondary thrombophilia (Table 3)

Sageshima, Transplantation 2022

Factors to be considered for repeated KTx

Infectious risk assessment

Polyoma virus, cytomegalovirus, Epstein-Barr virus, varicella zoster virus, human papilloma virus, Pneumocystis pneumonia, mycobacteria, recurrent urinary tract infection

Malignancy risk assessment

Posttransplant lymphoproliferative disorders, Kaposi's sarcoma, prior cancer recurrence

Psychosocial assessment

Nonadherence, psychological counseling, social worker evaluation

Peritransplant surgery

Surgical approach

Ipsilateral vs contralateral iliac fossa, retroperitoneal vs intraabdominal, orthotopic, transplant nephrectomy of previous graft

Arterial inflow and venous outflow

Degree and laterality of atherosclerosis, iliac or vena cava thrombosis, unconventional vascular anastomoses (eg, mesenteric or splenic vessels)

Ureteral anastomosis

Bladder capacity and function, intravesical, extravesical, uretero-ureterostomy

Risk mitigation strategy for individual risk identified during workup

Anticoagulation, antimicrobial, other pharmaceutical intervention, plasmapheresis

Sageshima, Transplantation 2022

Outcomes of third and subsequent KTx

Study	Number of patients	1-y/5-y patient survival	1-y/5-y graft survival	Comments
Redfield, UNOS, 2015[21]	2492 (third)	–/–	–/70% (third DD) –/79% (third LD) –/76% (first DD) –/86% (first LD)	Higher DGF rate: 33% (third DD) and 7% (third LD); more early (≤30 d) graft losses; better graft survival in patients who maintained second graft >5 y
Assfalg, Eurotransplant, 2020[22]	206 (≥fourth)	92%/78% (≥fourth DD)	93%/68% (≥fourth DD)*	*Patients with primary nonfunction were excluded from graft survival analyses.*
	956 (third)	96%/87% (third DD) 95%/85% (first DD)	94%/79% (third DD)* 98%/89% (first DD)*	Higher primary nonfunction rate: 13%; younger patients and more favorable HLA matches than first graft
Hagan, Dublin, 2003[23]	2 (fifth) 9 (fourth) 38 (third)	100%/97% (third/fourth/fifth)	0%/0% (fifth) 67%/55% (fourth) 90%/62% (third)	Poor graft survival in highly sensitized patients; AR and CAN as dominant causes of graft failure; rare surgical graft loses
Loupy, Paris, 2007[24]	56 (third) 301 (second) 1965 (first)	98%/96% (third) similar (first/second)	91%/72% (third) similar (first/second)	More sensitized patients, all third received induction therapy; lower graft survival with AR or CNI-free maintenance; higher rate of surgical complications
Blanco, Madrid, 2009[25]	30 (third)	97%/86% (third)	87%76% (third)	70% with hepatitis C infection; graftectomy performed in most patients; poor graft survival in hypersensitized and early previous graft losers
Horovitz, Ontario, 2009[26]	28 (third) 28 (first)	93%/83% (third) 96%/87% (first)	78%/66% (third) 78%/75% (first)	Paired donor analysis; more sensitized patients; more induction therapy; higher DGF (46%) and AR (50%) rates
Izquierdo, Barcelona, 2010[27]	8 (fourth) 74 (third) 358 (second)	86%/86% (fourth) 93%/91% (third) similar to third (second)	71%/43% (fourth) 88%/76% (third) similar to third (second)	Chronic rejection and CAN as common causes of graft loss; significantly inferior fourth graft survival
Kienzl-Wagner, Innsbruck, 2011[28]	15 (fourth) 41 (third)	85%/– (fourth) 97%/89% (third)	69%/– (fourth) 73%/54% (third)	Mainly sensitized patients; 2-y patient/graft survival: 64%/47% (fourth); DGF/AR rates: 49%/44% (third) and 60%/33% (fourth)
Benkö, Essen, 2019[29]	1 (fifth)	96%/86% (third/fourth/fifth)	86%/70% (third/fourth/fifth)	More patients with atherosclerosis and sensitization in third/fourth/fifth; longer operative time and more thrombotic complications; DGF rate: 25% and AR rate: 37% in third/fourth/fifth
	16 (fourth) 91 (third) 108 (second)	95%/86% (second)	87%/75% (second)	
Dabare, London, 2019[30]	8 (fourth) 69 (third) 330 (second) 2154 (first)	–/90% (third/fourth) –/94% (second) –/92% (first)	–/74% (third/fourth) –/85% (second) –/89% (first)	Significantly inferior graft survival in second (hazard ratio: 1.32) and third/fourth (hazard ratio: 2.33); high DGF and thrombotic complication rates in third/fourth

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Risk factors for graft thrombosis

Inherited and acquired risk factors for graft thrombosis
Thrombophilia
Factor V Leiden
Prothrombin G20210A mutation
Protein C deficiency
Protein S deficiency
Antithrombin deficiency
Antiphospholipid syndrome
Lupus anticoagulant
Anticardiolipin antibody
Beta 2 glycoprotein-I antibody
Hyperhomocysteinemia
eg, MTHFR gene mutation, folate, vitamin B6/B12 deficiencies
Elevated factor VIII
Donor factors
Small graft (eg, pediatric donors weighing <7 kg with small arteries)
Multiple vessels
Donation after circulatory death
Expanded criteria donor
Prolonged ischemia time
Recipient factors
Personal history of unprovoked thromboembolism
Family history of thromboembolism (thrombophilia often inherit autosomal dominant)
Repeat transplant
Diabetes mellitus
Atherosclerosis
Hypotension
Erythrocytosis
Nephrotic syndrome
Peritoneal dialysis
Immunosuppressive medication
Calcineurin inhibitors, mTOR inhibitors, antibody induction

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Indications for kidney transplantectomy

Indications for allograft nephrectomy	
Before 12 months from transplantation	After 12 months from transplantation
Early graft loss	Signs of chronic infiammation
Vascular trombosis	Graft loss due to BK virus nephropathy and a high level of BK viraemia
Severe acute rejection	Graft intolerance syndrome
Hyperacute rejection	Cancer
Recurrent urinary infections or sepsis	Recurrent urinary infections or sepsis

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Early vs late start of dialysis in ESRD

Table 1. List of studies and trials comparing early with late start of dialysis treatment in patients with ESKD

Author/ study	Cohort	Follow-up	Main results
Gill *et al.* [8]	4741 with graft failure, returning to dialysis	15 ± 11 months	Four per cent higher mortality risk after return to dialysis for each 1 mL/min/1.73 m^2 higher eGFR at the time of dialysis initiation (HR 1.04; $P < 0.01$)
Molnar *et al.* [30]	747 with graft failure, returning to dialysis	1185 days	In an unadjusted model, each 1 mL/min/1.73 m^2 higher eGFR at dialysis reinitiation was associated with a 6% higher risk of death (HR 1.06; $P = 0.02$); in adjusted models, this finding was not significant (HR 1.02; $P = 0.54$)

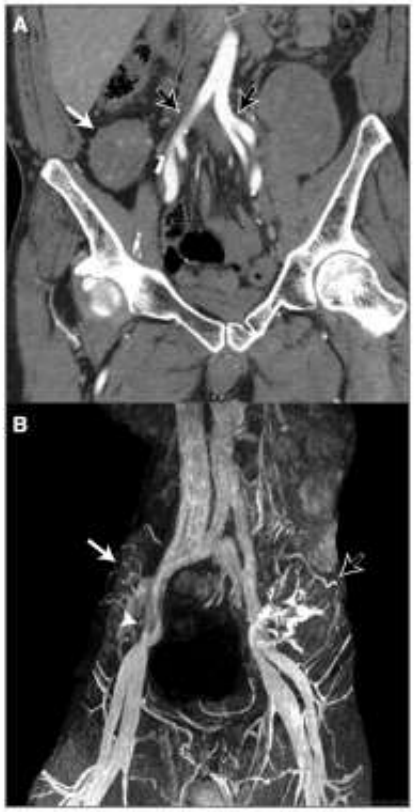
Fiorentino, CKJ 2020

PD vs HD in failed transplants

Author/ study	Cohort	Type of dialysis	Main results
Davies *et al.* [33]	45 patients with renal transplant failure	28 starting PD treatment and 17 starting HD treatment	No significant difference in the survival of failed transplant patients starting PD as compared with those starting HD (log rank: P = 0.11)
De Jonge *et al.* [34]	60 patients with renal transplant failure	21 starting PD treatment and 39 starting HD treatment	Death did not differ significantly between the two groups (P = 0.72). Moreover, there was a tendency towards higher patients' survival and re-transplantation tended to be more frequent in the PD post-transplant group
Perl *et al.* [36]	2110 patients with renal transplant failure	389 starting PD treatment and 1721 starting HD treatment	No difference in overall survival between HD- and PD-treated patients [HR (HD:PD) 1.05 (95% CI 0.85–1.31)], with similar results seen for both early and late survival.
Perl *et al.* [37]	16 113 patients with renal transplant failure	1865 starting PD treatment and 14 248 starting HD treatment	Survival in both groups was similar [HR for PD compared with HD 1.09 (95% CI 1.0–1.20)]. Compared with HD, PD is associated with an early survival advantage, inferior late survival and similar overall survival
Salazar *et al.* [38]	165 patients with renal transplant failure	16 starting PD treatment and 149 starting HD treatment	Survival prognosis, even adjusted by Charlson comorbidity index, death causes and retransplantation rate had no statistically significant difference

Fiorentino, CKJ 2020

Vascular issues



Fiorentino, CKJ 2020

Cohort

Table 1. Cohort characteristics (number of individuals in the analysis: 2346)

Variable	Statistic	Missing
Cohort characteristics at first graft loss		
Age, yr	44±14	0 (0%)
Women	917 (39%)	7 (<1%)
Duration of dialysis before first transplantation, yr	1.5 (0.7–3.1)	13 (<1%)
Year of first transplantation	1993 (1987–2001)	0 (0%)
Duration of first transplant, yr	5 (1–10)	0 (0%)
Panel reactive antibody, %	8 (0–40)	407 (17%)
Follow-up information		
No. of individuals with second transplantation	1869 (80%)	0 (0%)
Live donor organ second transplantation	115 (5%)	40 (2%)
Preemptive second transplantation[a]	79 (4%)	0 (0%)
Time from first graft loss to waitlisting for second transplantation, yr	0.6 (0.2–1.4)	0 (0%)
Time from first graft loss to second transplantation, yr	2.5 (1.2–4.2)	0 (0%)
No. of deaths during follow-up	966 (41%)	0 (0%)
Time from first graft loss to death, yr	7.8 (3.8–13.7)	0 (0%)
Follow-up time, yr	10.7 (5.3–18.8)	0 (0%)

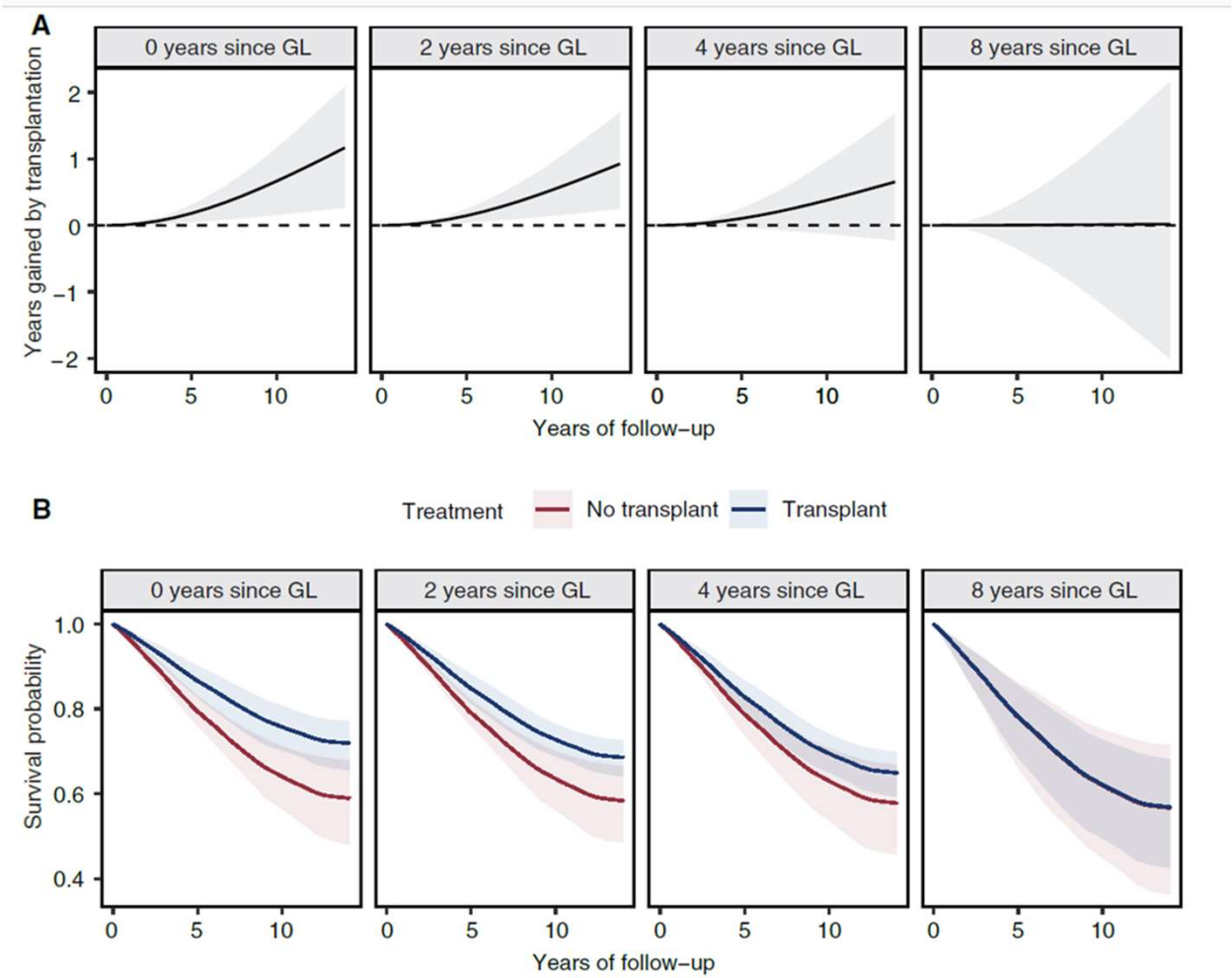
Kainz, CJASN 202217,90-97.

HR retransplant vs never retransplant

Figure 2. | Hazard ratio comparing the effect of the treatment strategies "retransplant" versus "never retransplant—remain on the waiting list with continued dialysis" on mortality, conditional on the waiting time in years elapsed since first graft loss. The haz-

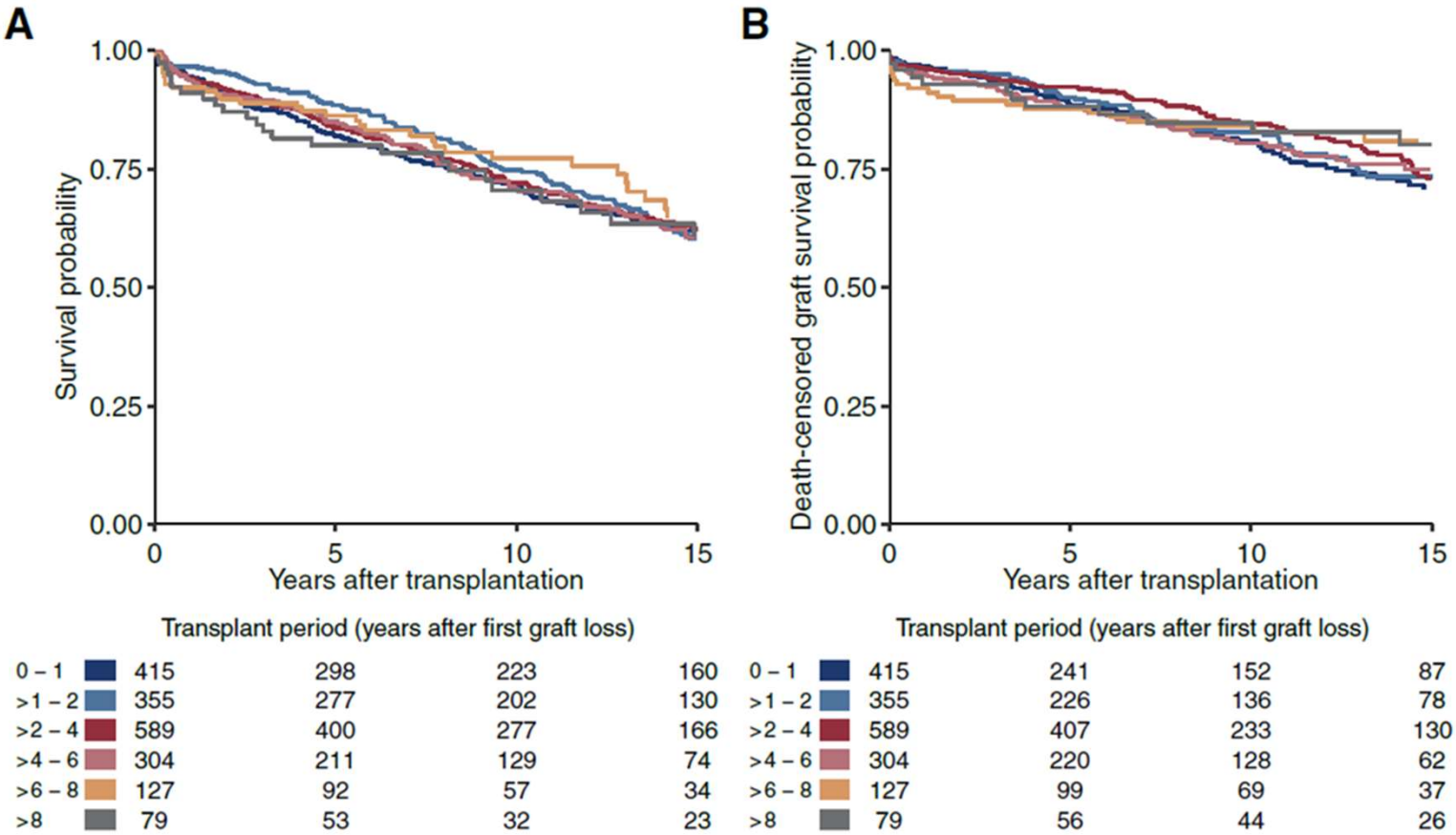
Kainz, CJASN 202217,90-97.

Survival outcomes graft



Kainz, CJASN 202217,90-97.

Patient and death-censored survival



Kainz, CJASN 202217,90-97.

Guideline 2.1 – Tx : Pre-transplant assessment UK 2011

We recommend that the object of pre-transplant assessment is:

a) to ensure transplantation is technically possible;
b) to ensure the recipient's chances of survival are not compromised by transplantation;
c) to ensure that graft survival is not limited by premature death (maximum benefit obtained from a limited resource);
d) to ensure pre-existing conditions are not exacerbated by transplantation;
e) to identify measures to be taken to minimise peri- and post-operative complications;
f) to inform patients of likely risks and benefits of transplantation. (1C)

Guideline 2.3 – Tx : Preparation of the renal transplant recipient UK 2011

We suggest that the use of pre-operative beta-blockers may be considered in patients at high cardiovascular risk undergoing renal transplantation but must be introduced at least 1 month before transplantation. Beta-blockers should not be discontinued abruptly peri-operatively. Low dose aspirin therapy is not a contraindication to transplantation and can be continued peri-operatively. (2C)

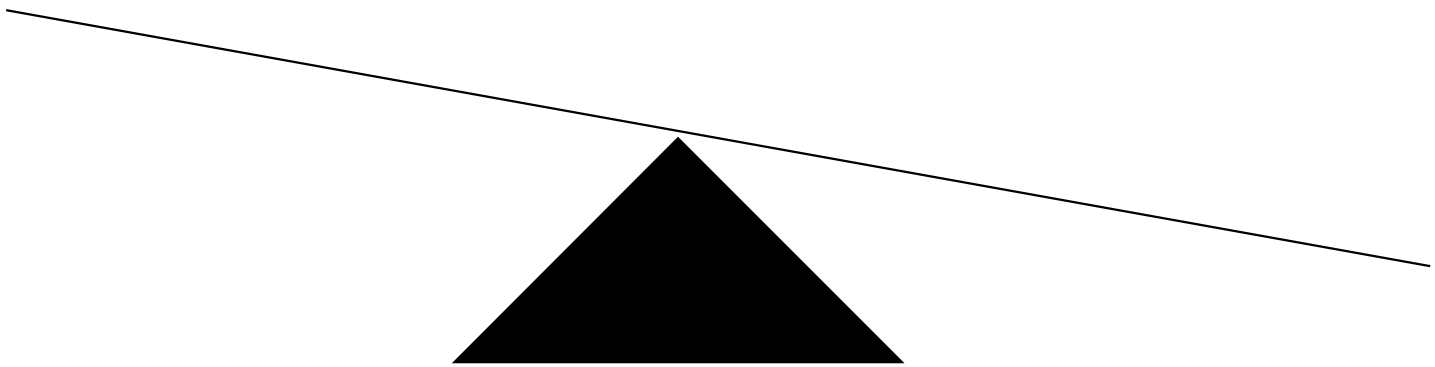
Guideline 2.5 – Tx : Preparation of the renal transplant recipient UK 2011

We recommend that obese patients (BMI >30 kg/m^2) present technical difficulties and are at increased risk of peri-operative complications. They should be screened rigorously for cardiovascular disease and each case considered individually. Although obesity is not an absolute contra-indication to transplantation, individuals with a BMI >40 kg/m^2 are less likely to benefit. (1B)

The paradox of transplantation

COMPLICATIONS

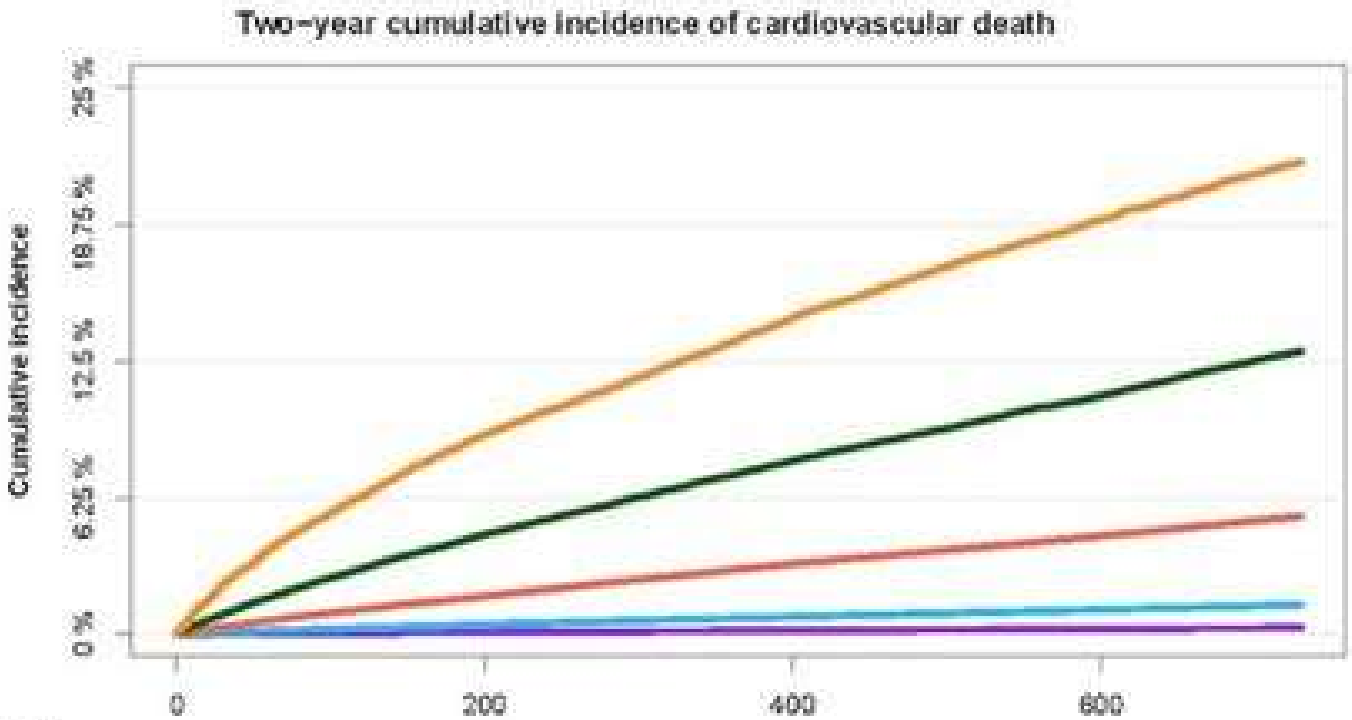
REJECTION



OVER-IMMUNOSUPPRESSION

UNDER-IMMUNOSUPPRESSION

Cardiovascular death and renal function



Kidney function (eGFR [ml/min/m2])									
90+	1826419	1775032	1731221	1677324	1621110	1561559	1505864	1432878	1348965
60-89	1273001	1247474	1226880	1202961	1176251	1143878	1111376	1065499	1009677
45-59	192285	187487	183755	179987	175915	171237	166334	159732	150980
30-44	58523	55655	53529	51594	49706	47747	45611	43169	40082
<30	17570	15897	14804	13993	13187	12350	11609	10932	9957

Take away messages

- Similar survival rates for retransplantation
- Reinitation on eGFR alone is not indicated
- Continuation of low-dose immunosuppression is appropriate/beneficial for the risk of de novo allosensitization
- Allograft nephrectomy should be considered only after an accurate balance of indications and contra-indications