Poor outcome in second kidney transplantation: a delayed event
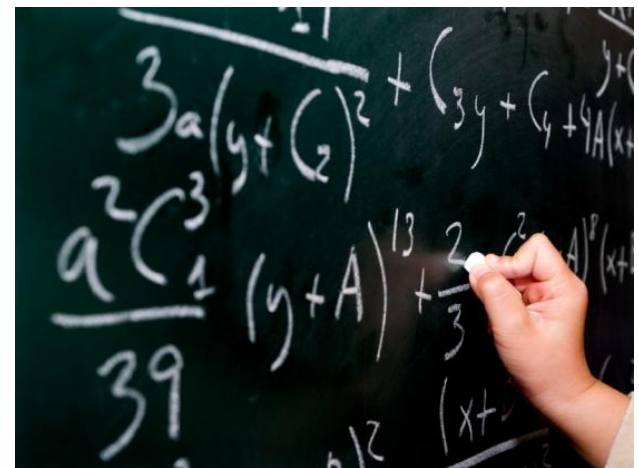
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Are patient and graft survival of first and second kidney transplant recipients comparable or not?
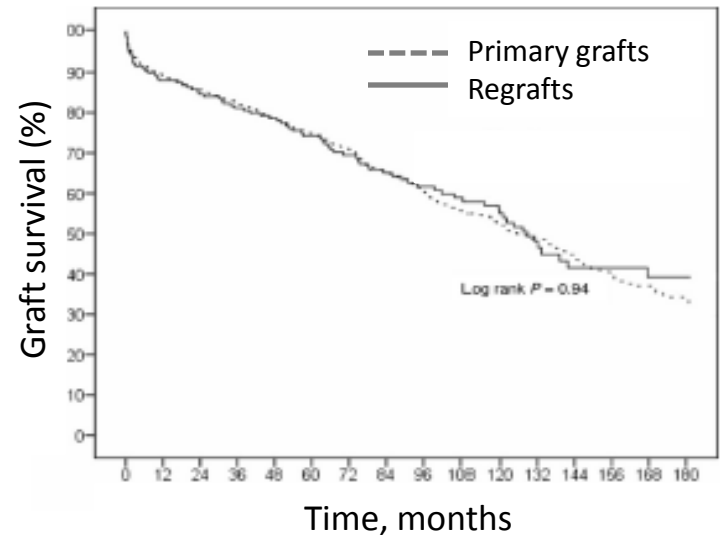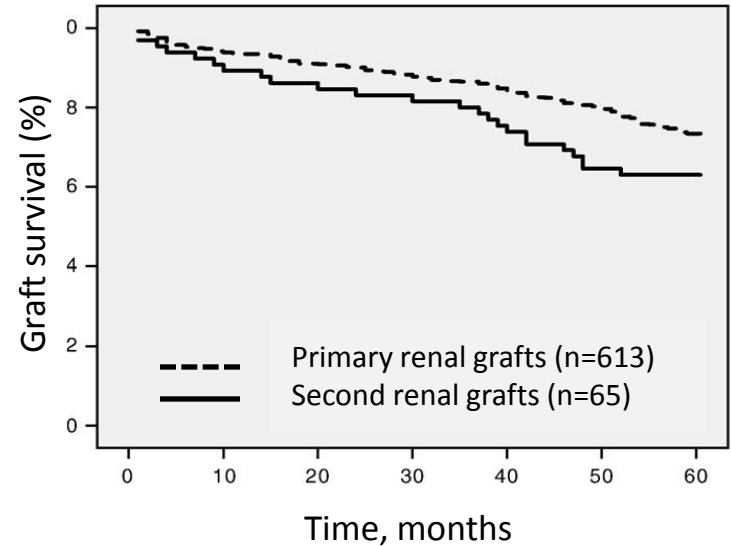
In recent studies :

> ## Excess risk in second graft?
>
> **(Magee et al. AJT 2007)**
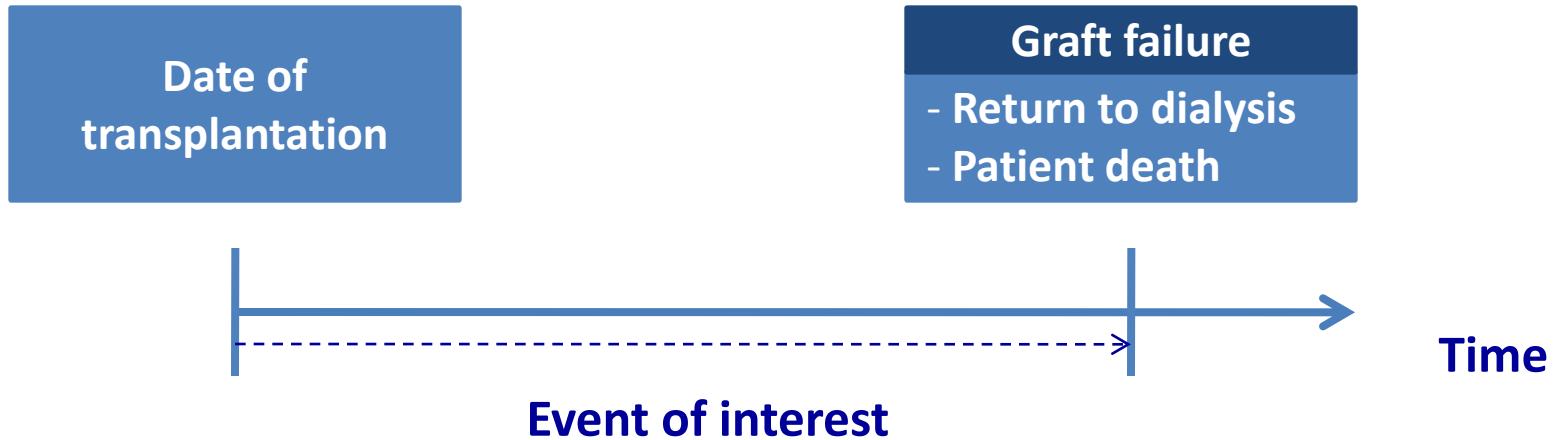> **(Wang et al. Transpl Immunol 2009)**

OR

> ## No difference between primary and second graft?
>
> **(Coupel et al. Kidney Int 2003)**
> **(Arnol et al. Transplantation 2008)**
> **(Gruber et al. Surgery 2009) …**

Graft survival (%) vs Time, months — Primary renal grafts (n=613), Second renal grafts (n=65)

Graft survival (%) vs Time, months — Primary grafts, Regrafts. Log rank *P* = 0.94

The study endpoint was the patient and graft survival

| Date of transplantation		Graft failure
		- Return to dialysis
		- Patient death

Event of interest

Time

Inclusion Criteria

DIVAT database

- **Centers: Nantes, Necker, Nancy, Toulouse, Montpellier or Lyon**
- **Adult recipients**
- **First or second grafts**
- **Transplanted from 1996**
- **Under MMF and steroids at transplantation**
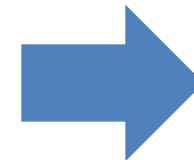
N = 3112 patients

Analysis methods were standard

Crude survival
Kaplan-Meier Method

and

Adjusted survival
Cox model Method
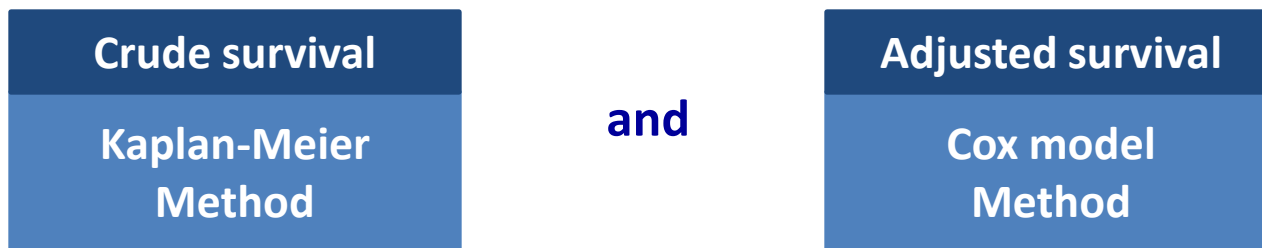
Cox model: adjustment on confounding factors

Recipient factors
- Gender and age - Causal nephropathy - Anti-class I and anti-class II PRA - Comorbidities (history of diabetes, cardiovascular disease, hypertension, dyslipemia, B or C hepatitis and malignancy)

Donor factors
- Age

Transplantation factors
- Transplantation period - HLA-A-B-DR mismatches - Relation donor/recipient - Cold ischemia time - Induction therapy

Results - Differences in demographic characteristics

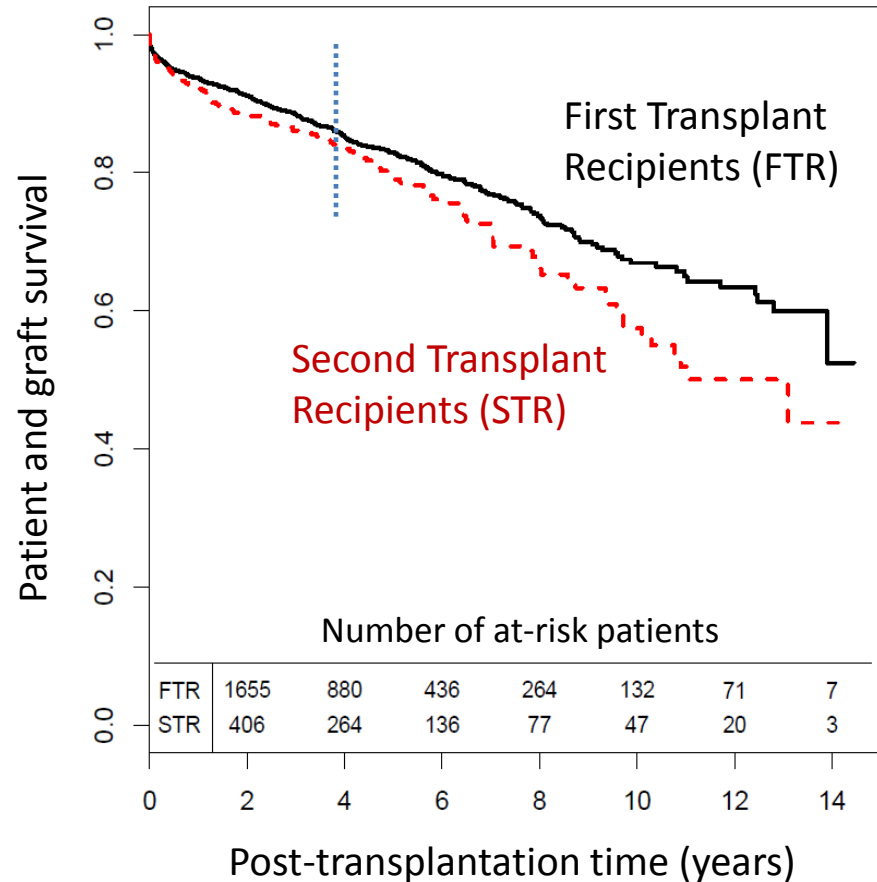| Variables	First grafts N = 2462 (79.3%)	Second grafts N = 641 (20.7%)
Recipient ≥ 55 years of age	44.7%	30.4%
Donor age ≥ 55 years of age	42.9%	32.6%
History of diabetes	12.0%	6.4%
More than 4 HLA-A-B-DRmismatches	15.8%	6.6%
Potentially recurrent causal nephropathy	30.2%	42.4%
Cold ischemia time ≥ 24 hours	27.1%	37.0%
Positive anti-class I PRA	17.1%	62.7%
Positive anti-class II PRA	16.7%	74.7%
Depleting induction therapy	35.9%	78.3%

PRA, panel reactive antibody; HLA, human leukocyte antigen

Results - Patient and graft survival is significantly lower for second transplant recipients

Log-rank: p = 0.0127

=> 2 periods?
The difference between FTR and STR seems to increase after 4 years

First Transplant Recipients (FTR)

Second Transplant Recipients (STR)

Patient and graft survival

Number of at-risk patients

FTR	1655	880	436	264	132	71	7
STR	406	264	136	77	47	20	3

Post-transplantation time (years)

# The Cox model confirmed that second transplantation is an independant risk factor of graft failure after 4 years

Variables	Hazard Ratio	95% CI	p
Graft rank before 4 post-graft years (2 / 1)	1.05	0.75-1.47	0.7830
Graft rank after 4 post-graft years (2 / 1)	2.18	1.35-3.50	*0.0013
Transplantation period (< 2005 / ≥ 2005)	1.32	1.01-1.72	*0.0427
Recipient gender (male / female)	1.01	0.82-1.25	0.9364
Recipient age (≥ 55 years / < 55 years)	**1.49**	**1.17-1.89**	***0.0012**
Causal nephropathy (recurrent / non recurrent)	1.13	0.91-1.39	0.2734
History of diabetes (positive / negative)	1.28	0.96-1.71	0.0947
History of hypertension (positive / negative)	0.86	0.67-1.12	0.2665
History of vascular disease (positive / negative)	1.05	0.80-1.38	0.7449
History of cardiac disease (positive / negative)	1.34	1.09-1.65	*0.0057
History of dyslipemia (positive / negative)	1.16	0.93-1.45	0.1971
History of malignancy (positive / negative)	1.17	0.84-1.62	0.3483
History of B/C hepatitis (positive / negative)	1.06	0.72-1.57	0.7587
Level of HLA-ABDR mismatch (≥ 5 / < 5)	1.30	0.99-1.71	0.0639
Anti-class I PRA (positive / negative)	**1.43**	**1.11-1.85**	***0.0055**
Anti-class II PRA (positive / negative)	0.98	0.74-1.30	0.8970
Induction therapy (depleting / non depleting)	0.88	0.69-1.12	0.2852
Cold ischemia time (≥ 24h / < 24h)	1.18	0.95-1.45	0.1370
Donor age (≥ 55 years / < 55 years)	1.19	0.94-1.49	0.1459
Relation recipient/donor (deceased donor / living donor)	**2.19**	**1.35-3.57**	***0.0015**
BMI (≥ 30 kg.m^{-2} / < 30 kg.m^{-2})	**1.54**	**1.14-2.09**	***0.0050**
Donor EBV serology (positive / negative)	1.80	1.17-2.77	*0.0076

* p<0.05

Is the higher risk for second grafts after 4 years related to:
- a higher frequency of acute rejection episodes (ARE)?
- a higher frequency of steroid-resistant ARE?

Unadjusted survival
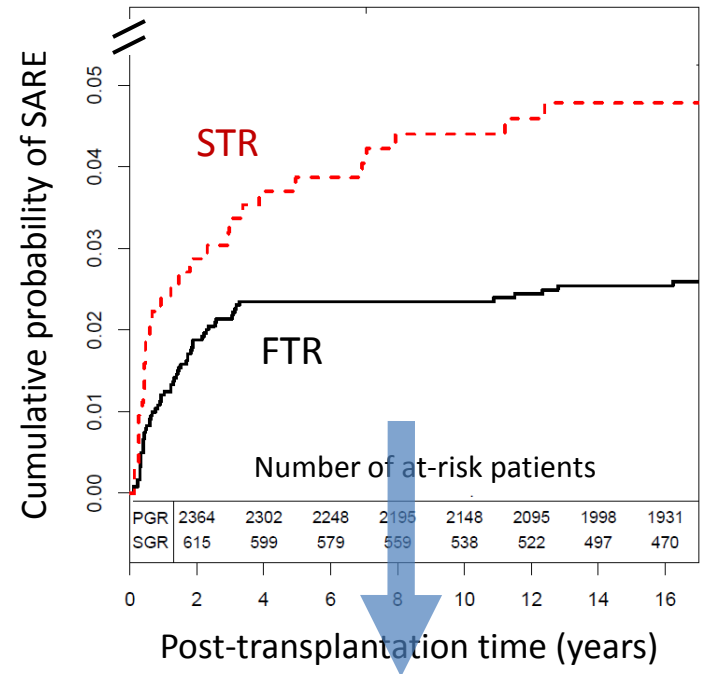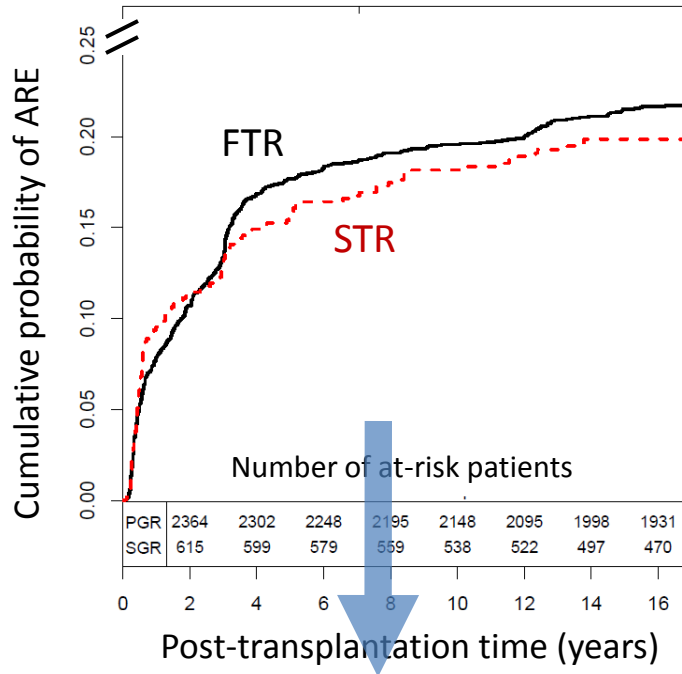
Cox model

HR = 1.01 (p = 0.9675)

Second transplant recipients don't tend to have a higher ARE occurrence than the first ones

HR = 1.27 (p = 0.4087)

Second transplant recipients tend to have a higher risk of steroid-resistant ARE (not significant)

Conclusion and prospects

After 4 post-graft years
Second kidney transplant recipients have more than twice as much risk of graft failure as the first ones

and

This time-dependent effect of graft rank seems unrelated to the frequency of ARE even the steroid-resistant ones

Potential hypotheses

UNDER CURRENT INVESTIGATION

Are ARE more deleterious for second transplant recipients once they have occurred?
⇒ **Multi-state model**

Is the occurrence of donor specific antibodies higher and/or earlier for second transplant recipients?
⇒ **Case control study**

Are acute rejection episodes more ABMR or high grade CMR for second transplant?
⇒ **Banff 2009 reread biopsy**