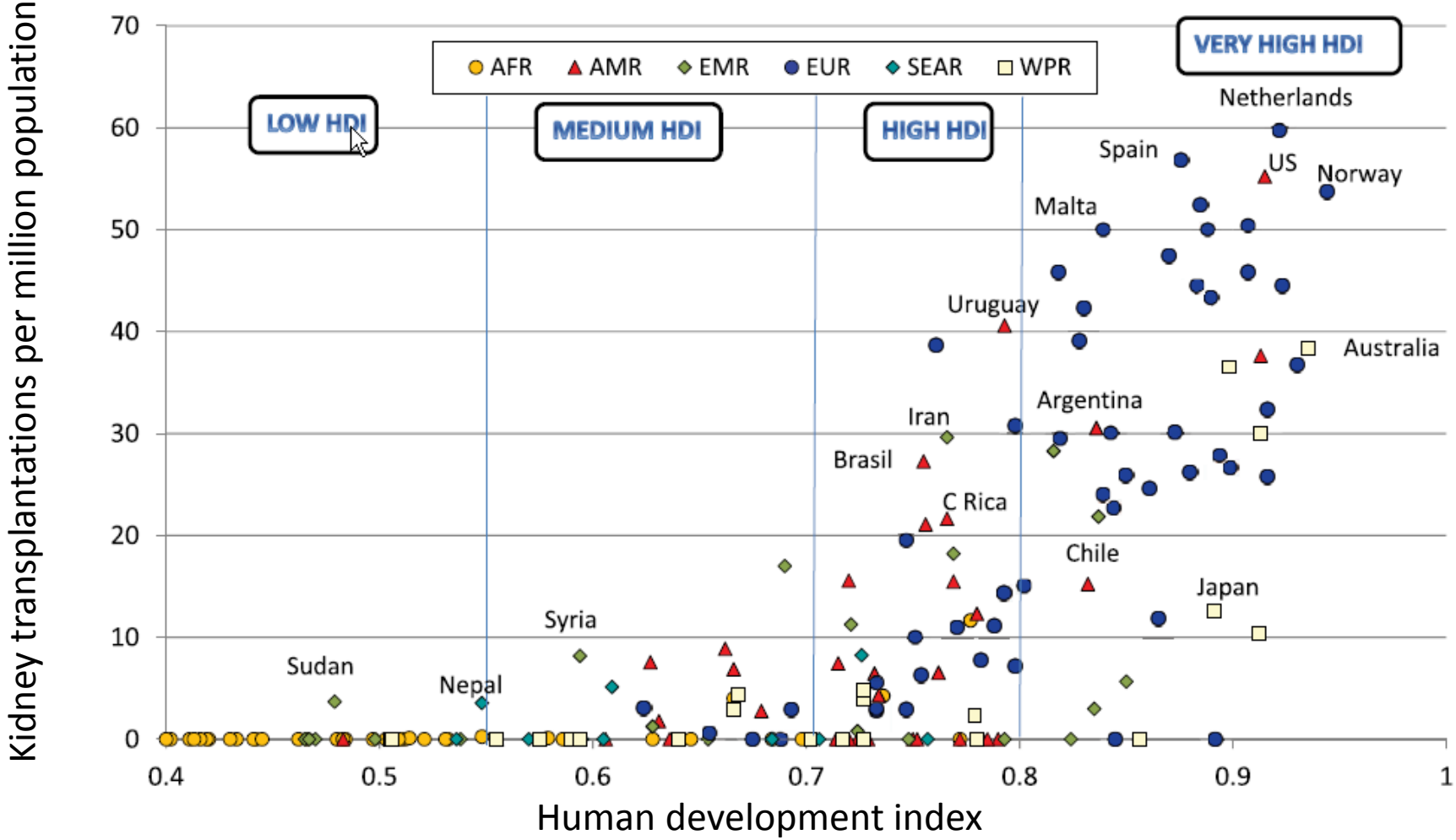
Personalized medicine in kidney transplantation, fact or fiction?

Dr JSF Sanders

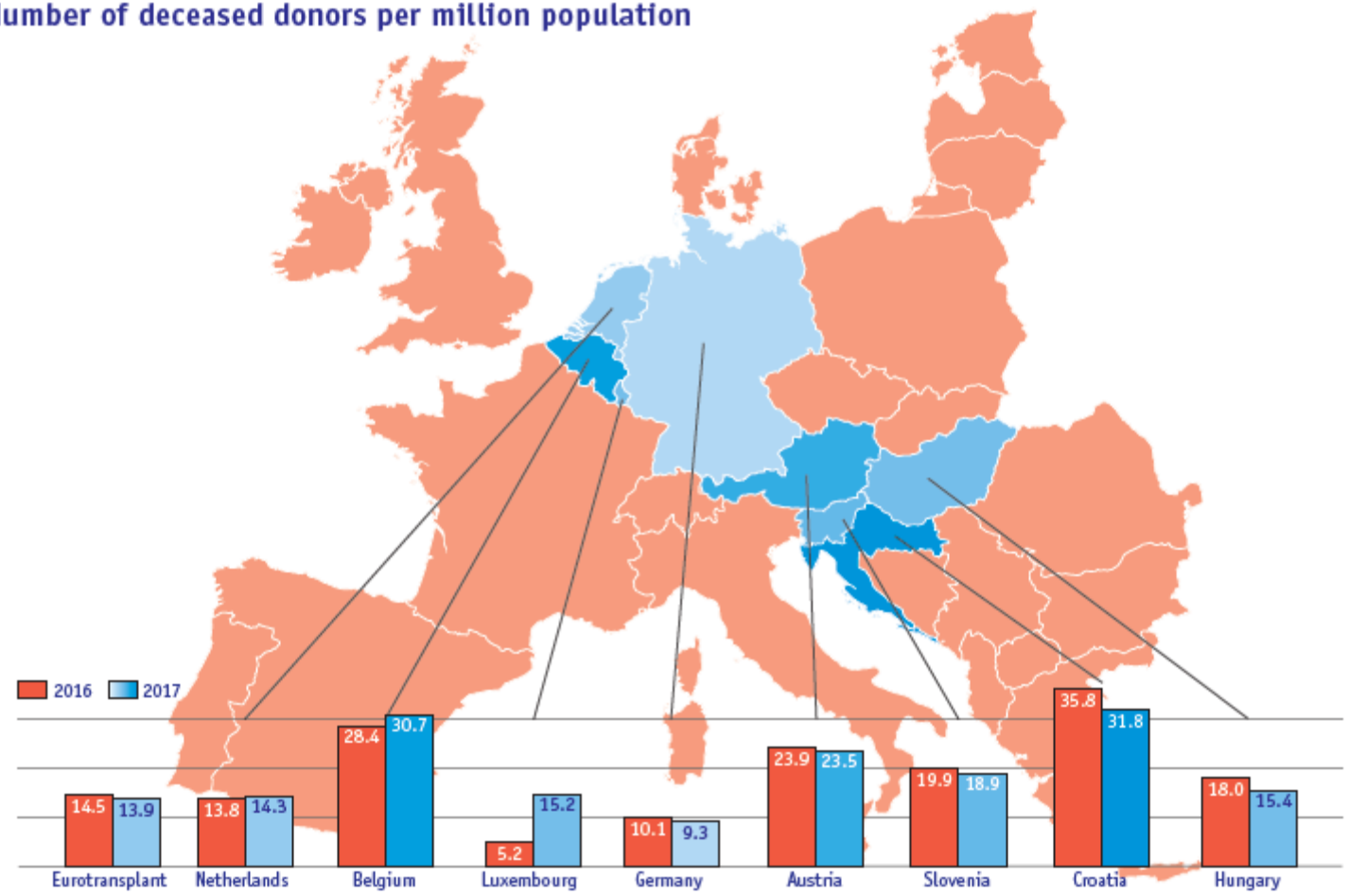
Worldwide inequality



Chapman JR AJKD 2017

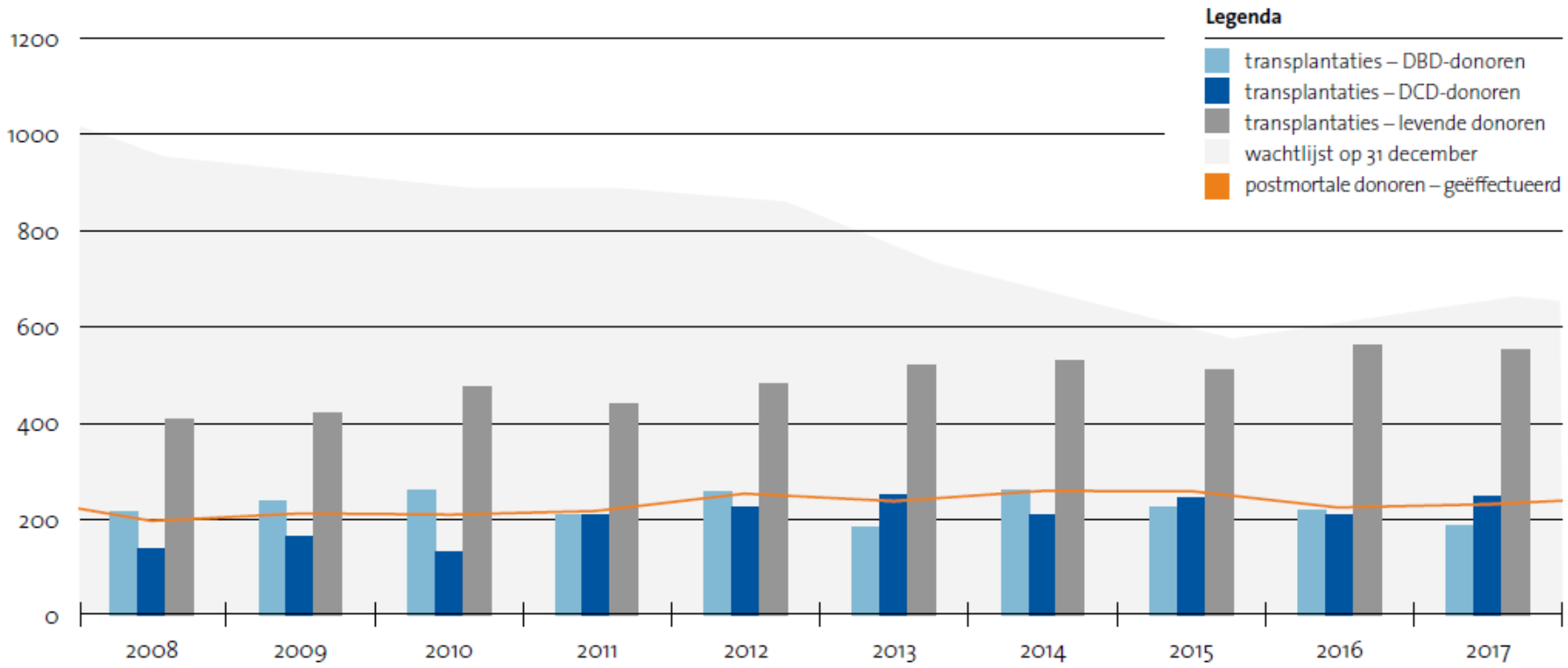
DONATION

Number of deceased donors per million population



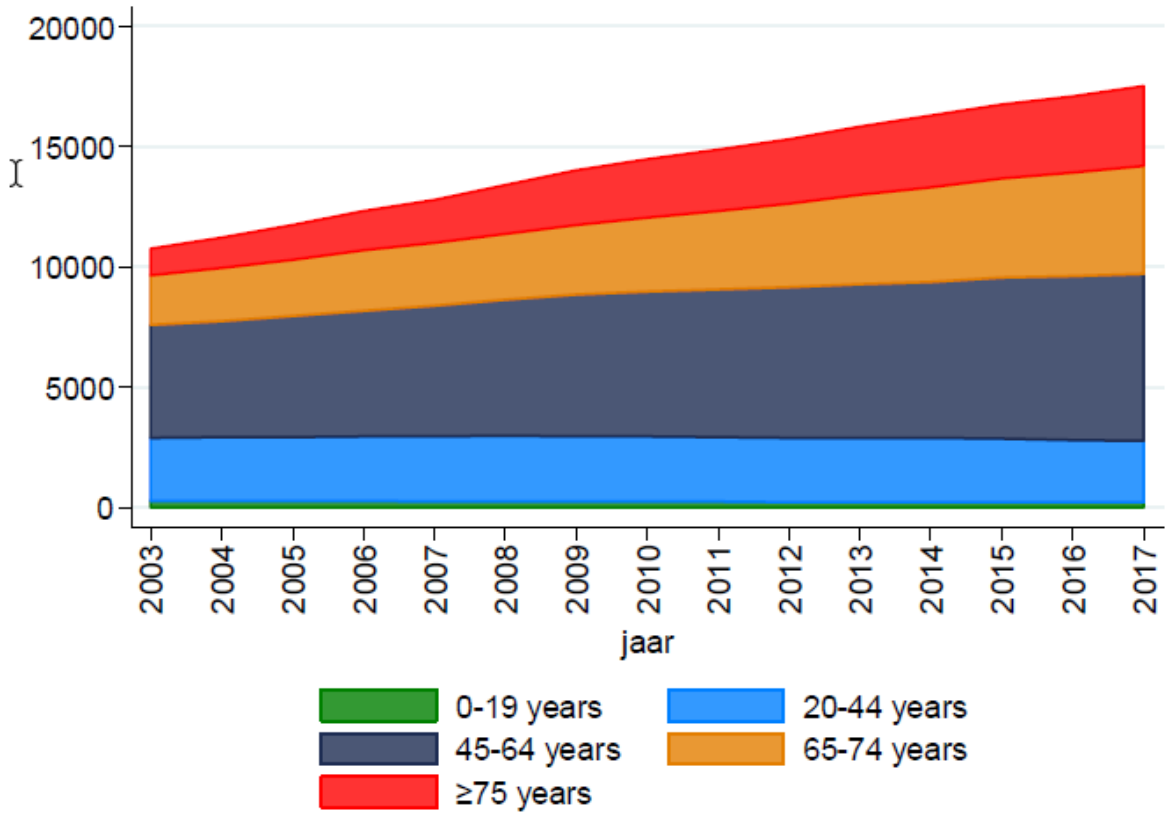
Eurotransplant Statistical Report

Waiting list development



Source: NTS

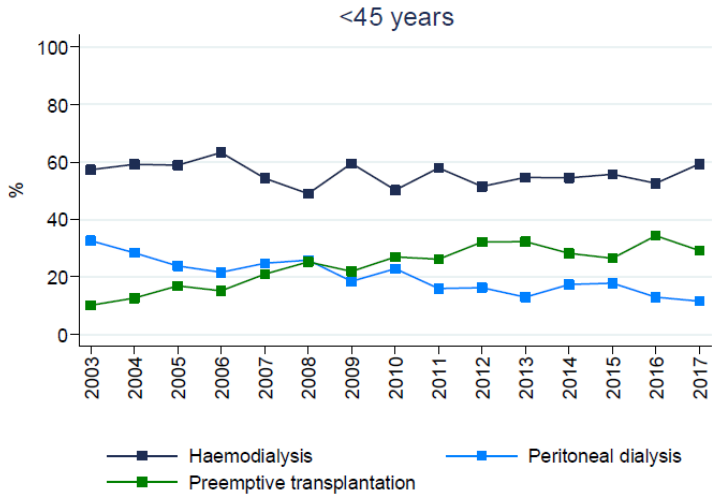
Prevalence of renal replacement therapy according to age groups

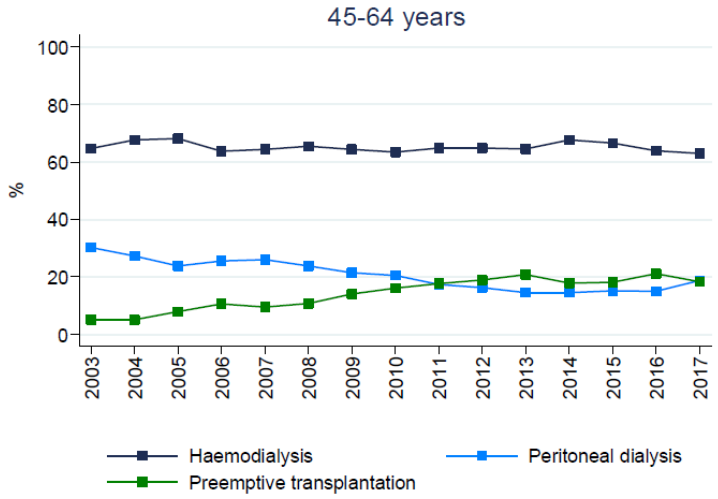


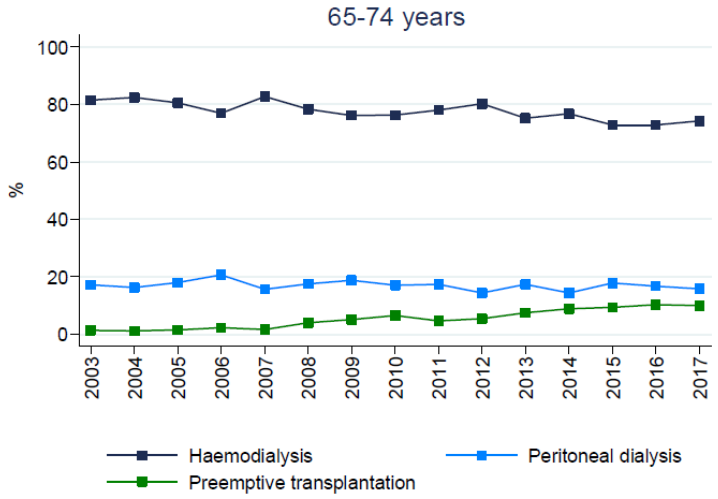
Source: nefrovisie

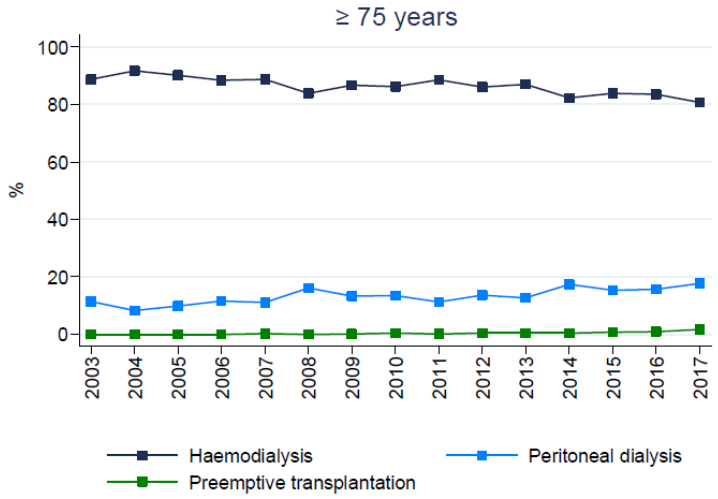
Age of renal transplant recipients at UMCG

Distribution of starting modalities



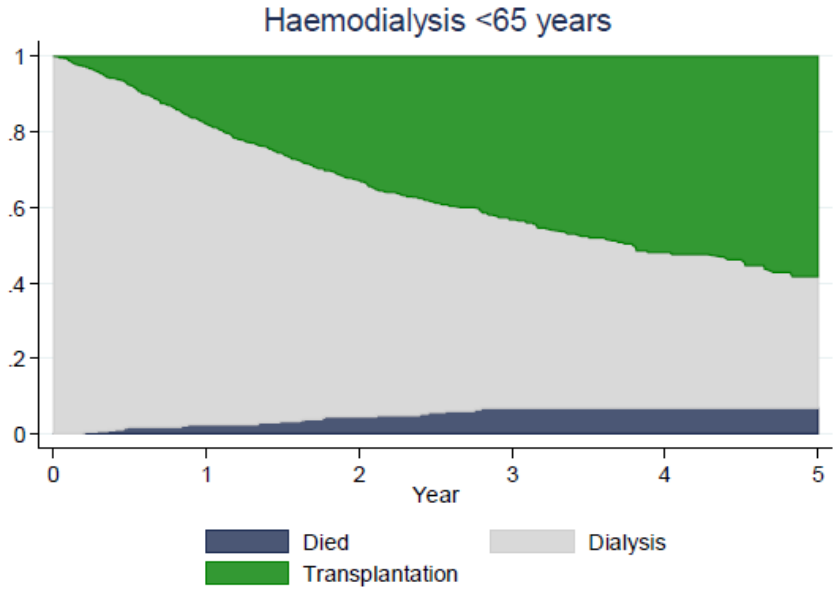


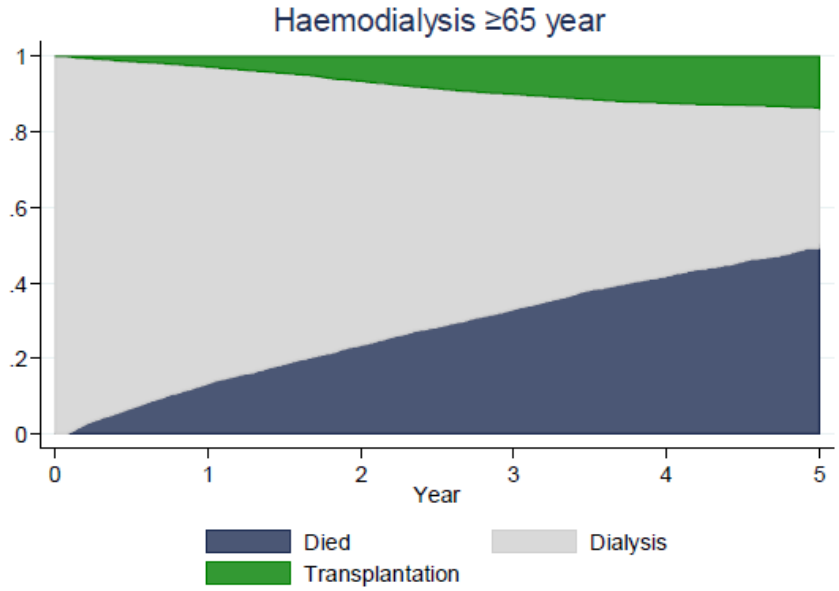




Source: Nefrovisie

Outcome of haemodialysis patients





Source: nefrovisie

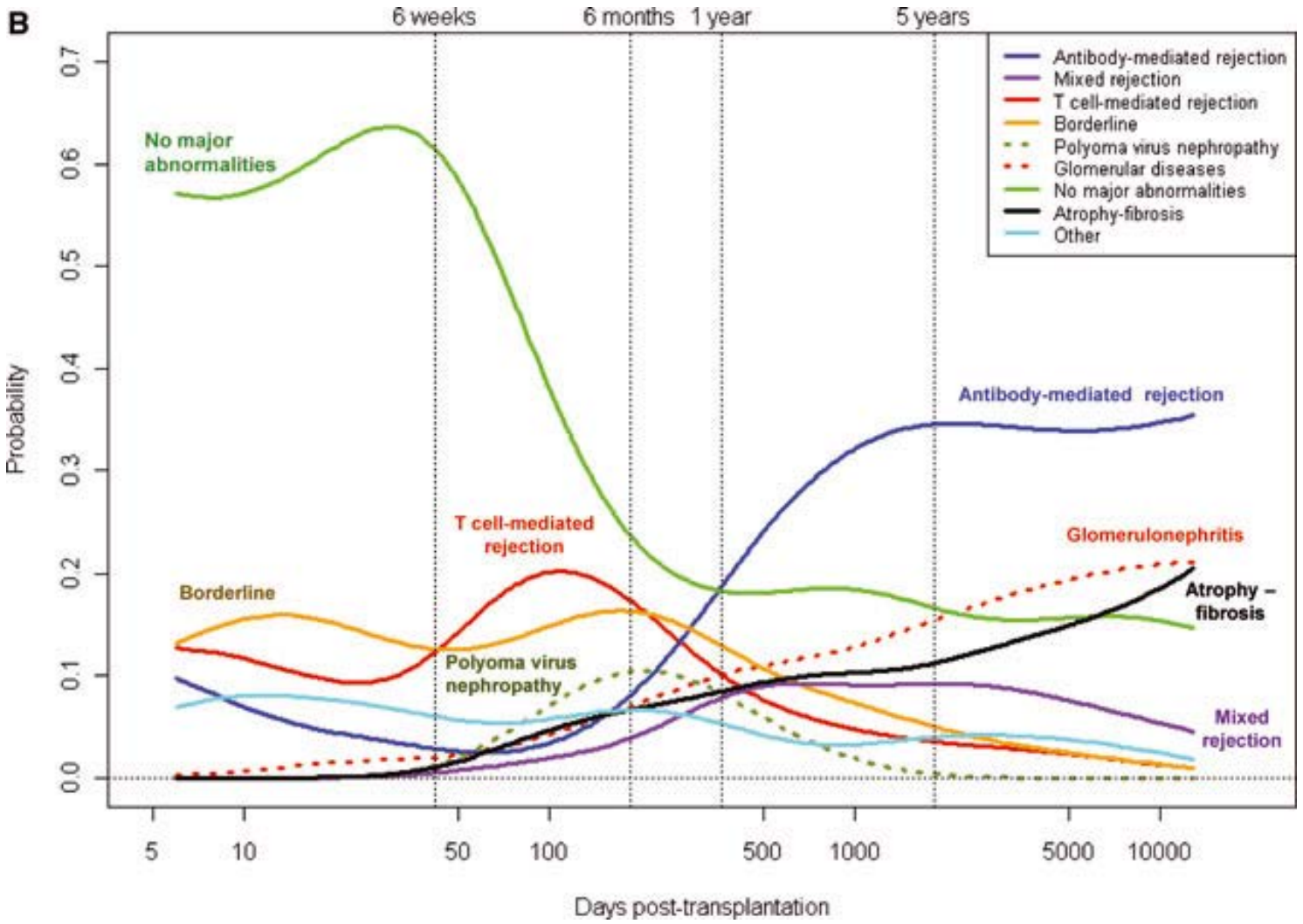
Dialysis duration before kidney transplantation UMCG

The Netherlands – current situation

- Too many patients dialyse too long

- More postmortal donors (new law)
- Better education (kidneyteam at home)
- ABO-i and HLA-i programs
- Further development of cross-over program
  - Give immunised patients more priority
- Further improvement of outcome

Why are kidneys lost?



Sellares, AJT 2012

Adherence

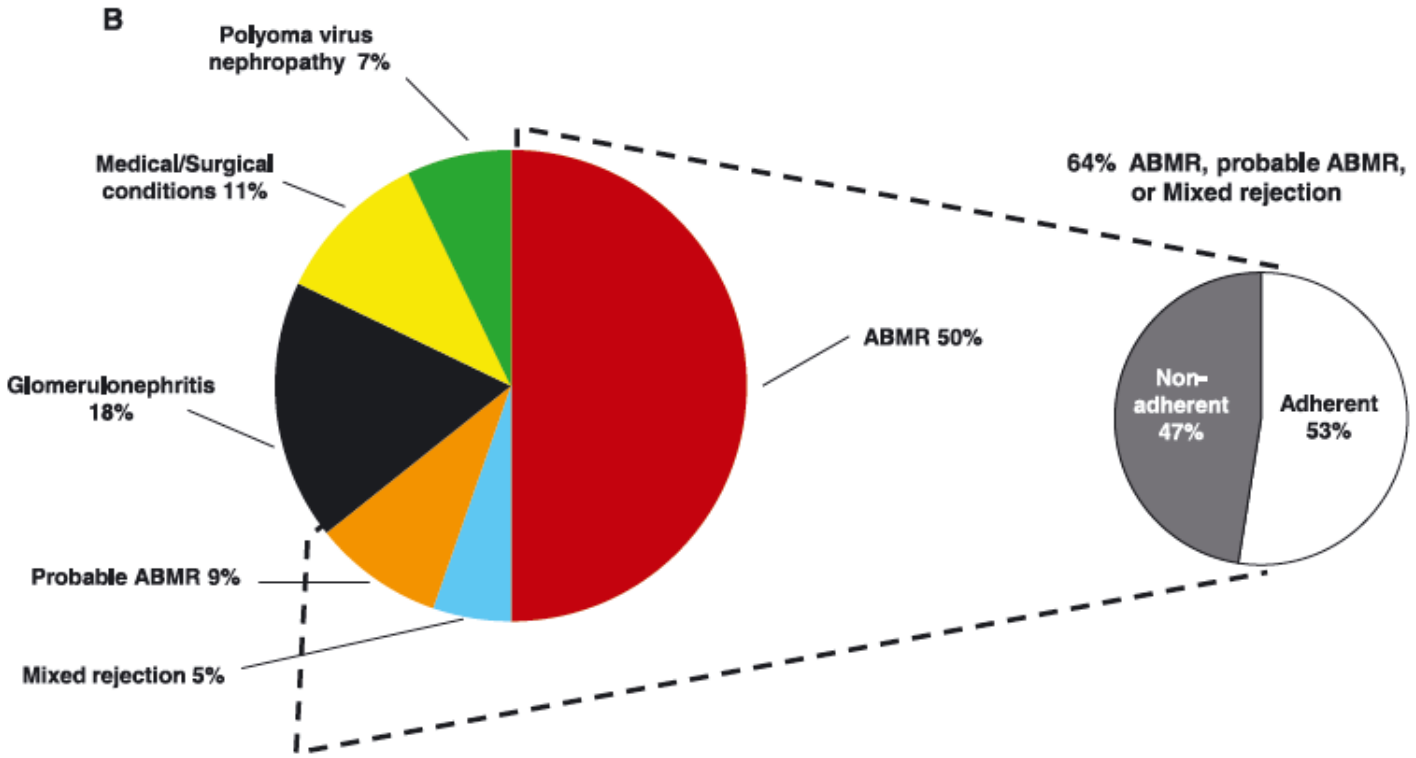
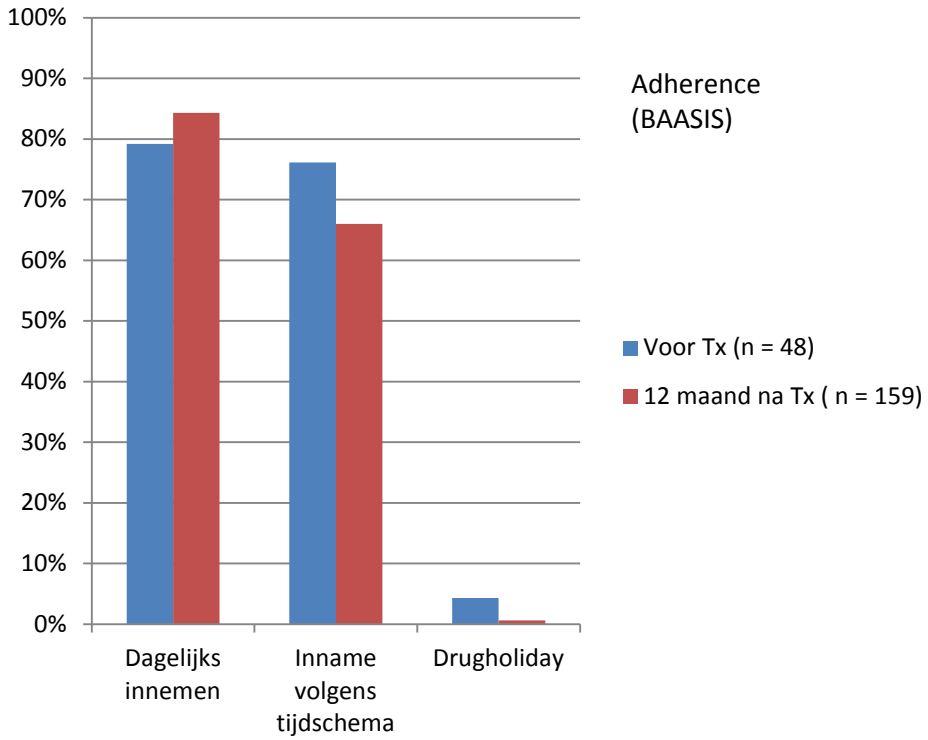
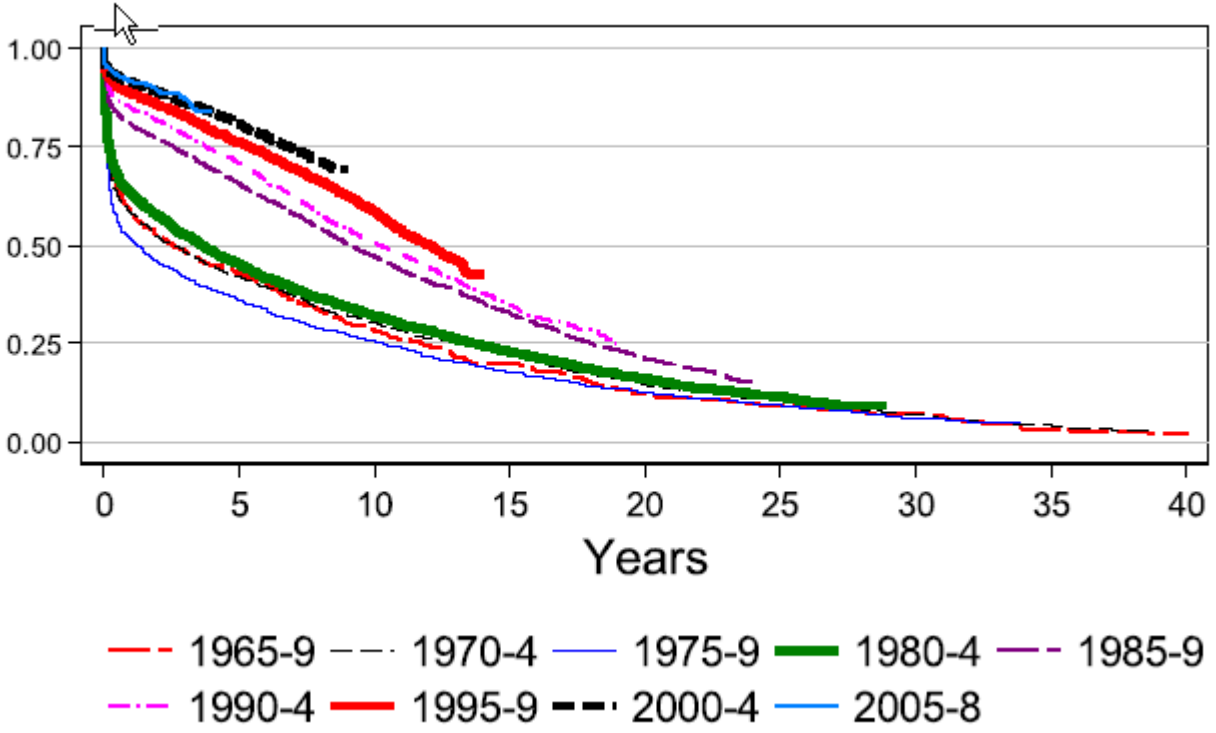


Figure 3: Attributed causes of graft failure in the biopsy-for-cause population. (A) Distribution of the attributed causes of failure (columns) according to the histological diagnosis in the last biopsy available per patient (rows). (B) Distribution of attributed causes of failure. Failures that could not be attributed due to missing clinical information are not represented (n = 4).

Adherence

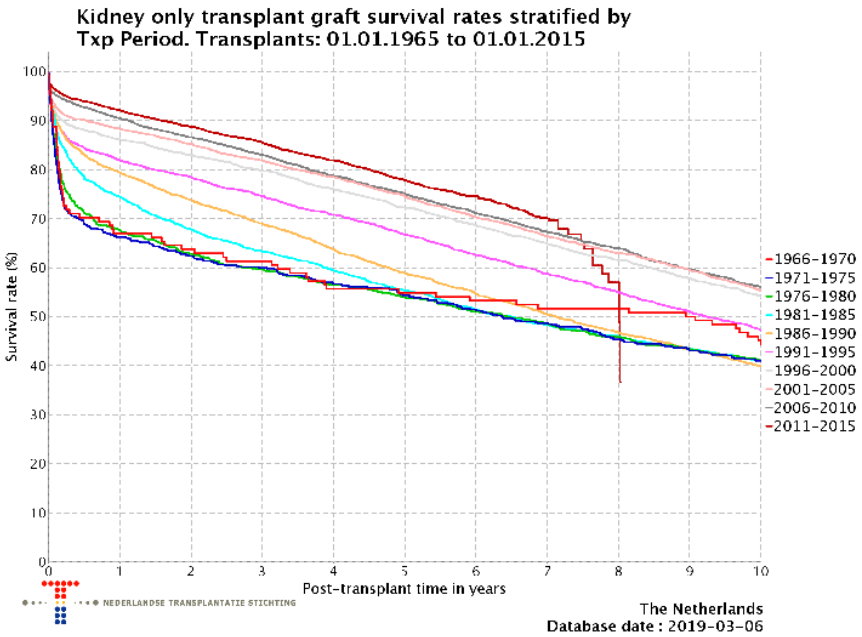

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Dagelijks innemen
Inname volgens tijdschema
Drugholiday
Adherence (BAASIS)
Voor Tx (n = 48)
12 maand na Tx (n = 159)

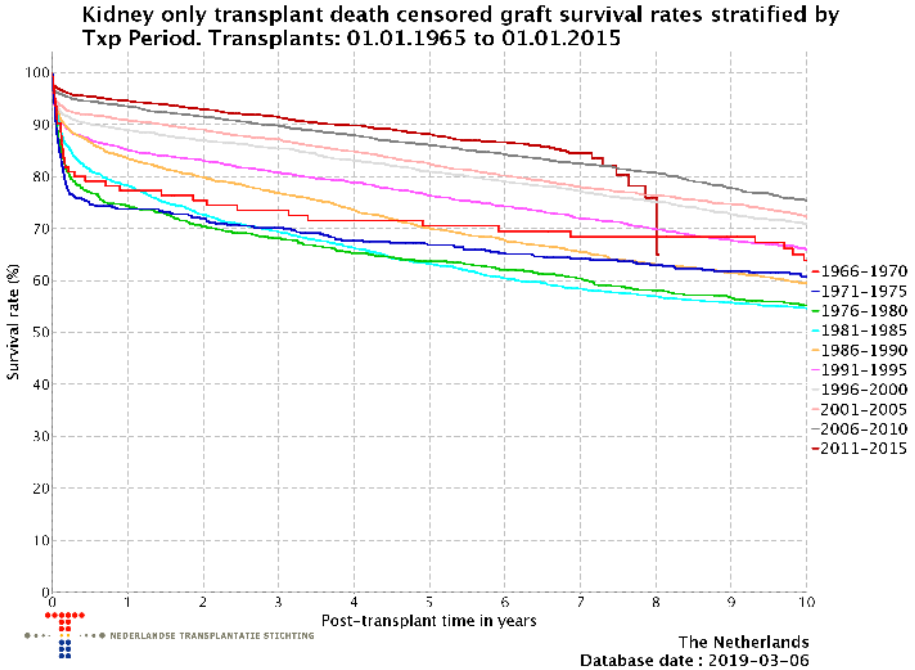
Graft survival of postmortem RTR in Australia-New Zealand



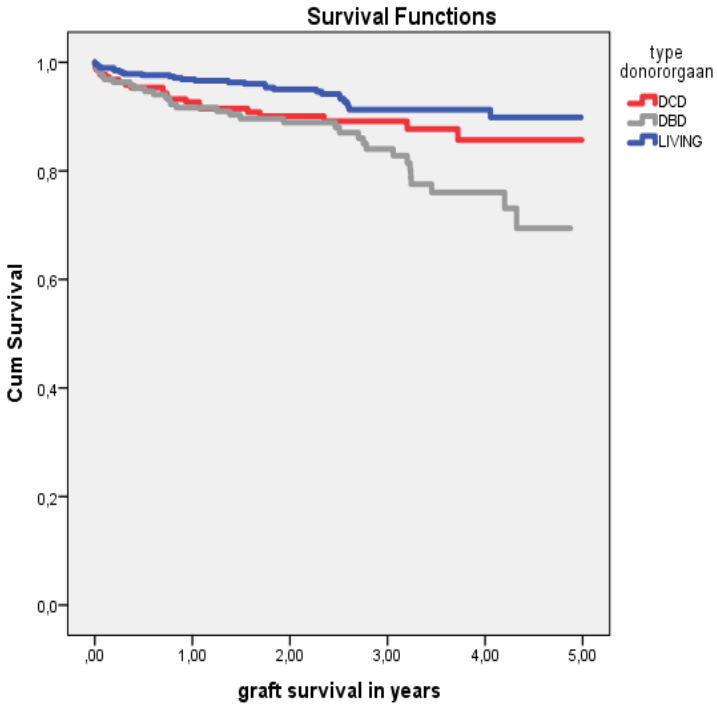
Source: ANZDATA Registry

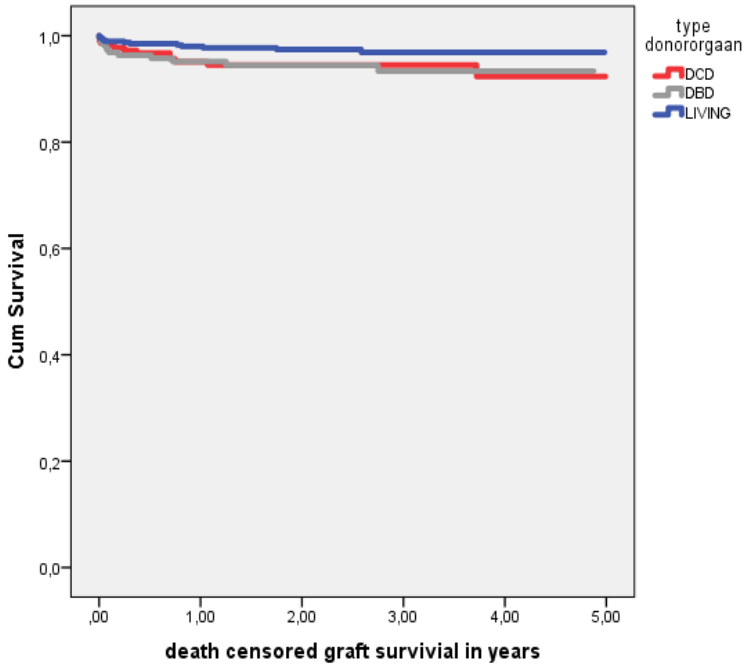
Graft survival Netherlands



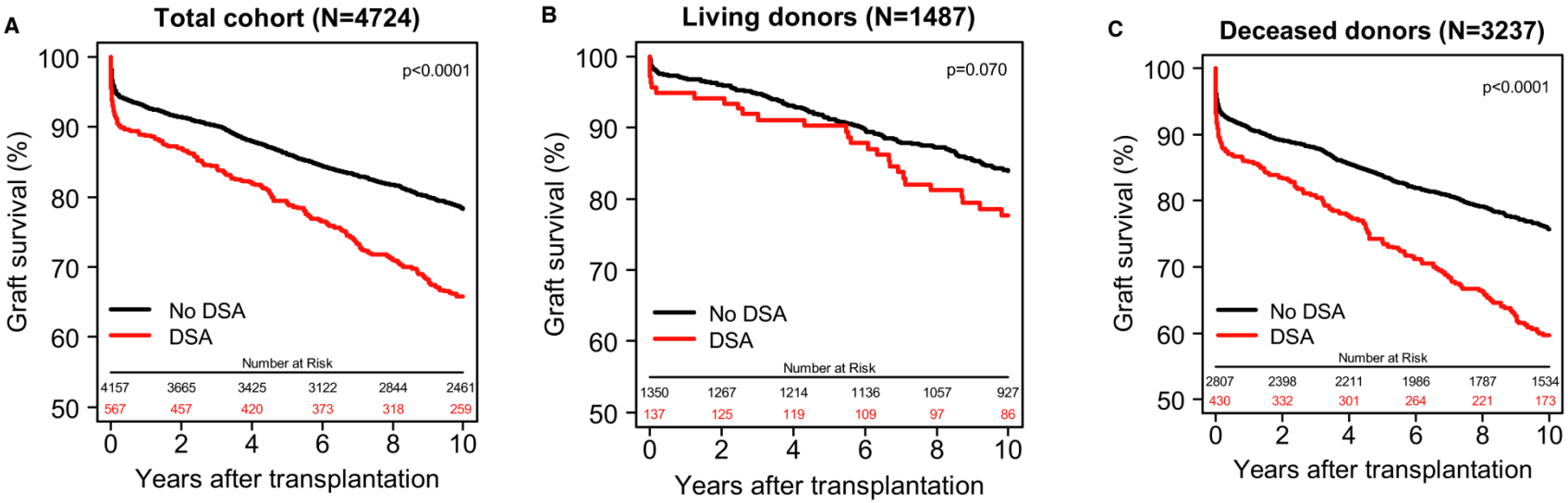


Current graft survival UMCG 2013-2017





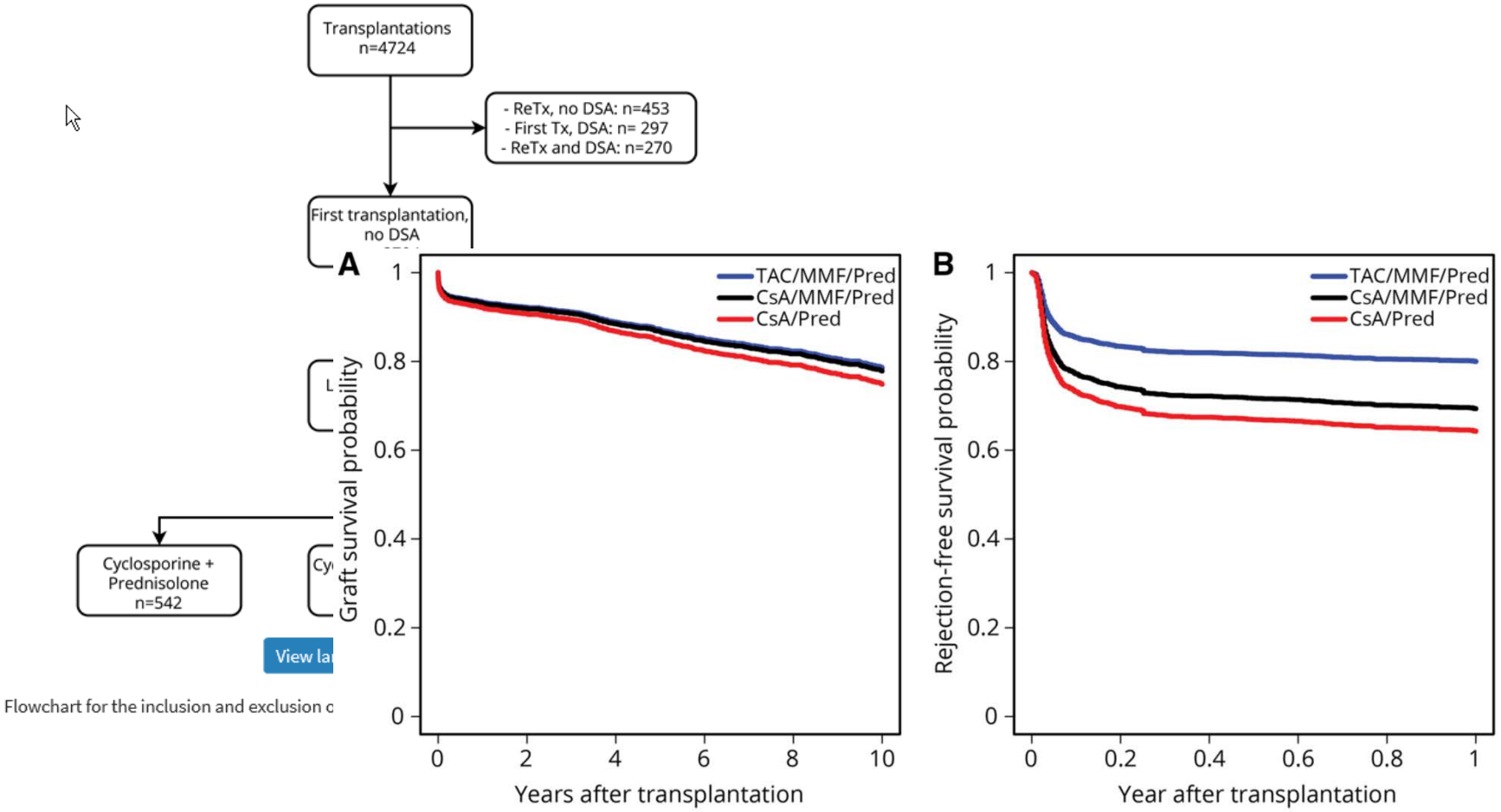
Differential effects of DSA in living versus deceased donor transplant recipients



Kamburova, AJT 2018

Survival according to initial immunosuppressive treatment

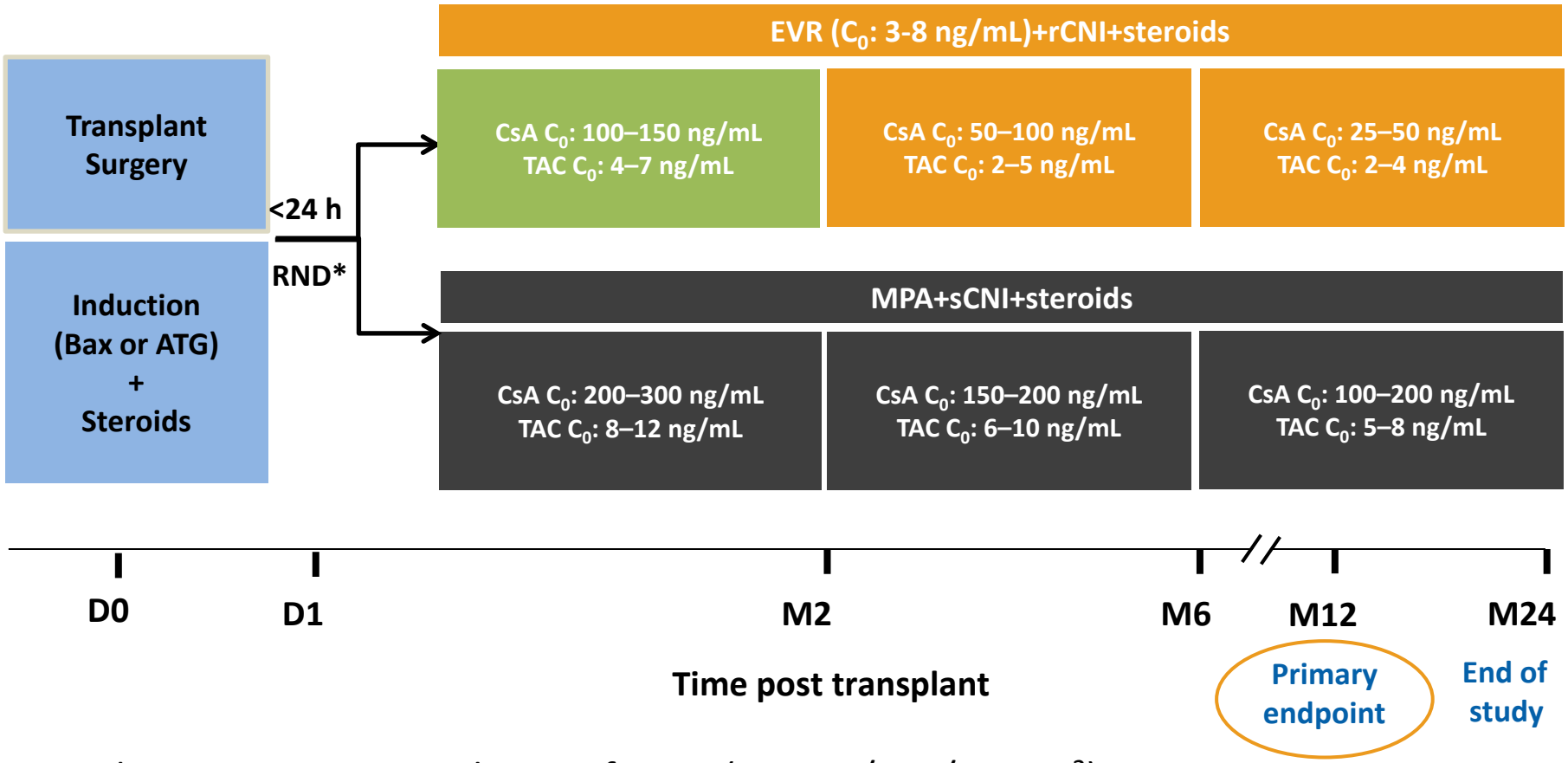
FIGURE 1



Michielsen LA, NDT 2018

Transform

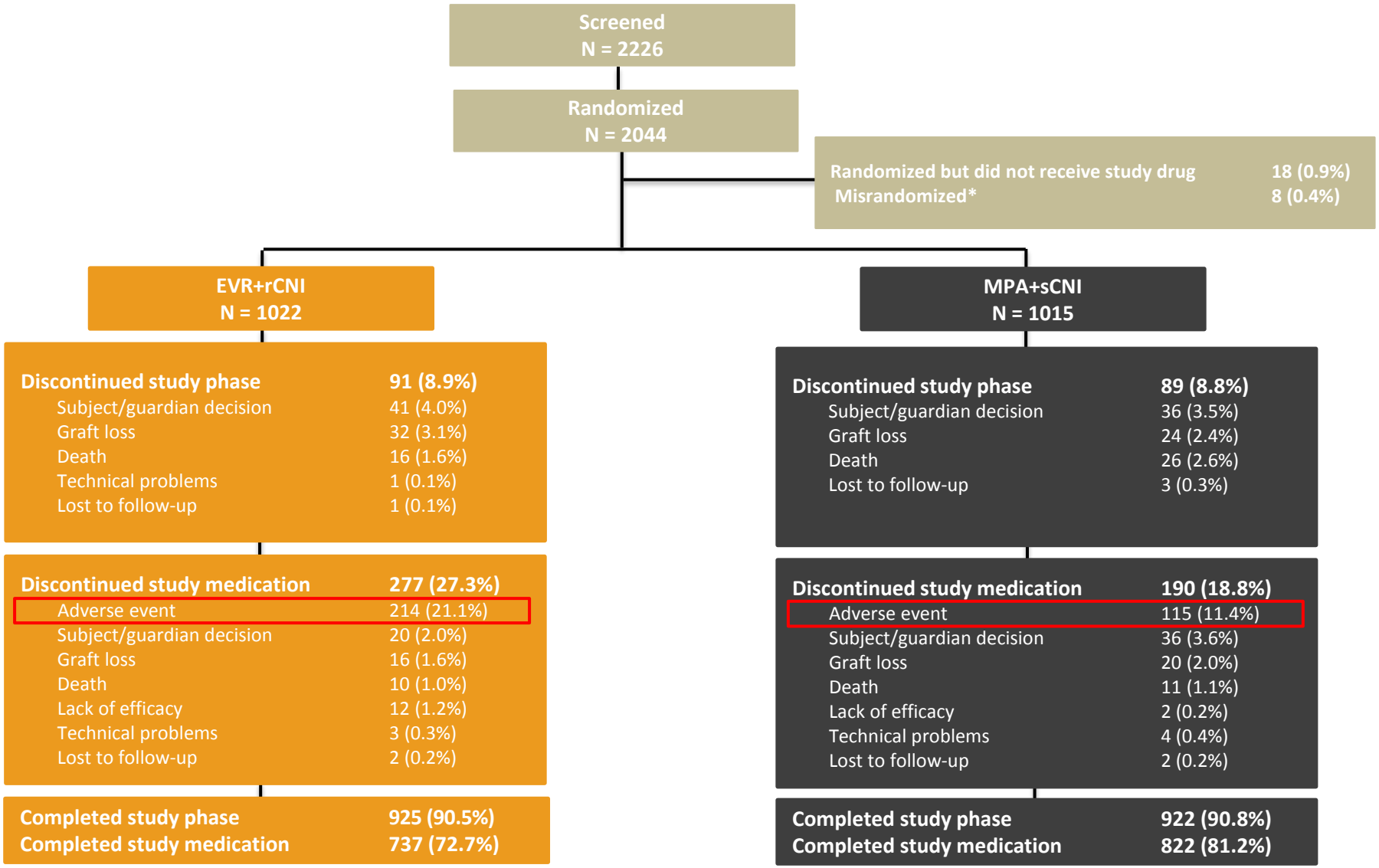
Largest randomized, multicenter, open-label, parallel group study to-date



binary composite endpoint of eGFR (<50 mL/min/1.73 m^2) or tBPAR

Pascual J, JASN 2018

Patient disposition



*one miscoded patient received study medication

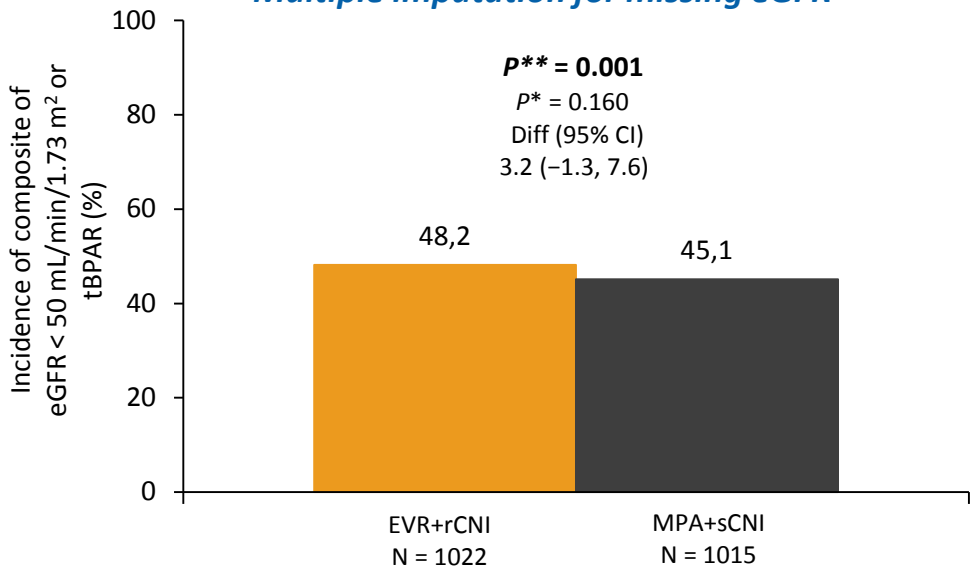
EVR, everolimus; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor

Primary efficacy endpoint

EVR+rCNI was non-inferior to MPA+sCNI

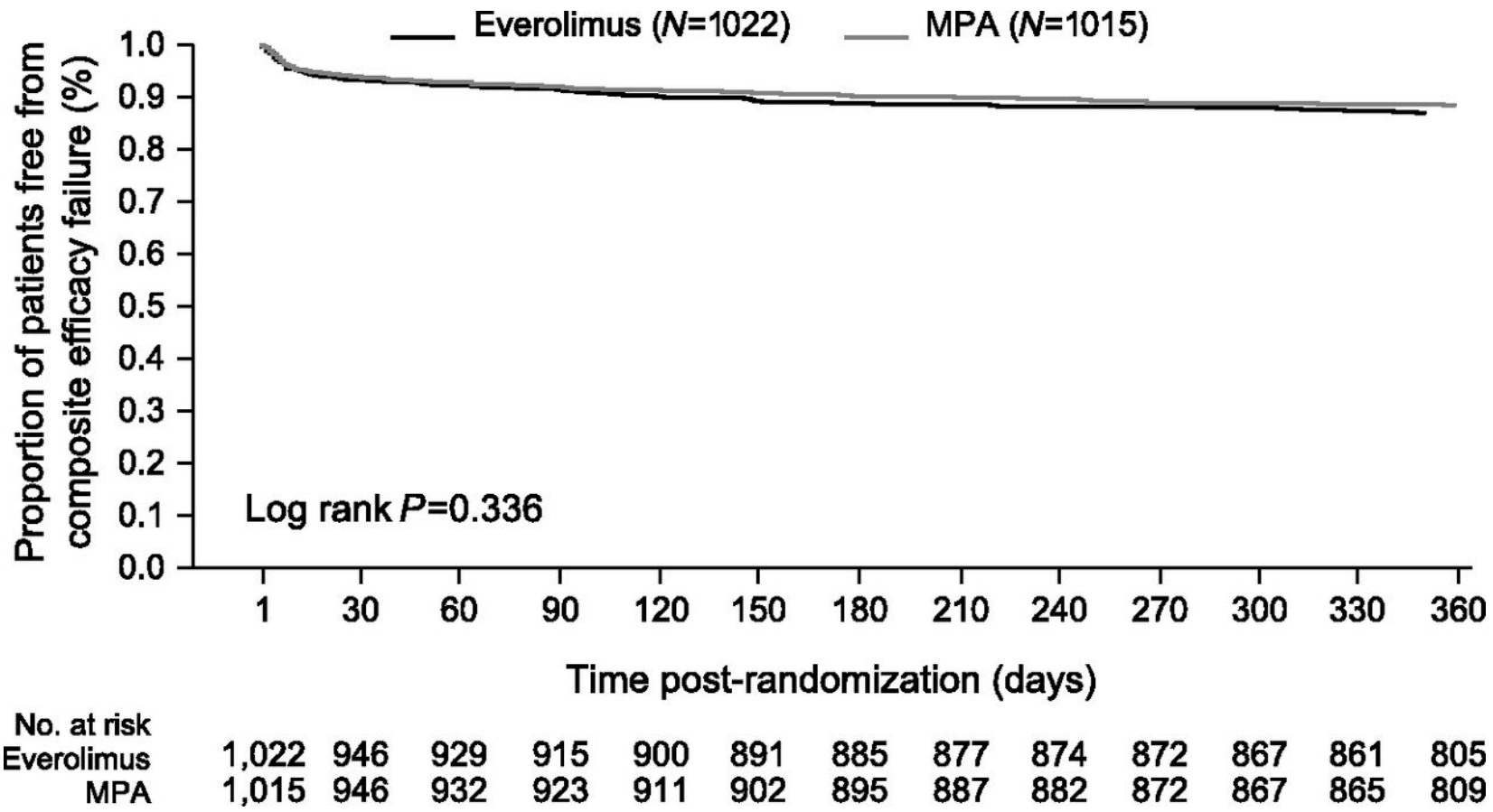
Full analysis set – M12

Multiple imputation for missing eGFR



Control-based imputation for missing eGFR Primary efficacy endpoint, FAS	EVR+rCNI N = 1022	MPA+sCNI N = 1015	Difference (95% CI)	*P** value
eGFR < 50 mL/min/1.73 m² or tBPAR† , n (%)	491 (48.0)	457 (45.0)	3.0 (−1.4, 7.4)	0.185

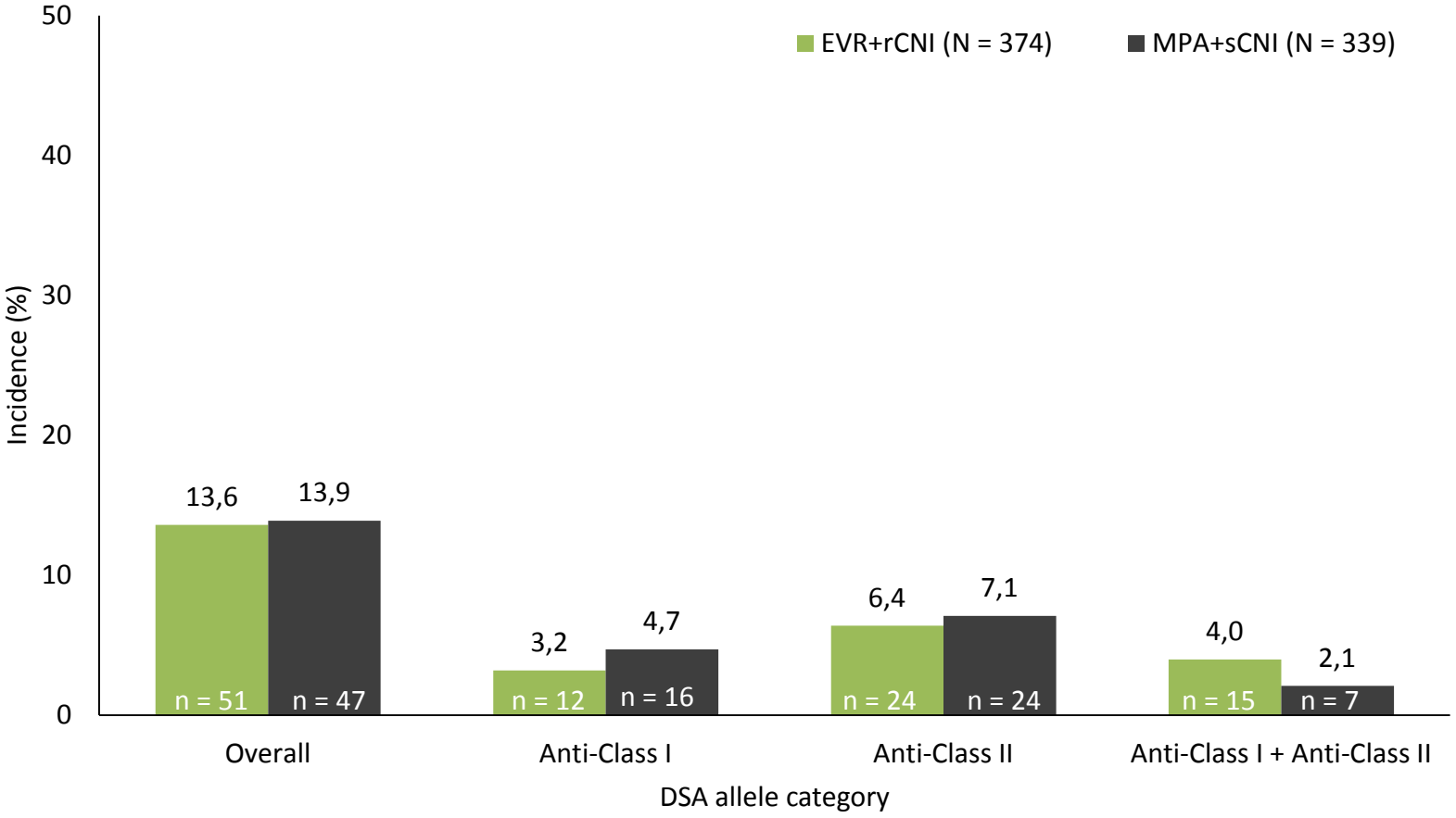
Key secondary endpoint of tBPAR, graft loss or death at month 12 post-transplant was 14.9% versus 12.5% in the everolimus versus MPA groups,



DSA

Incidence was balanced between both groups

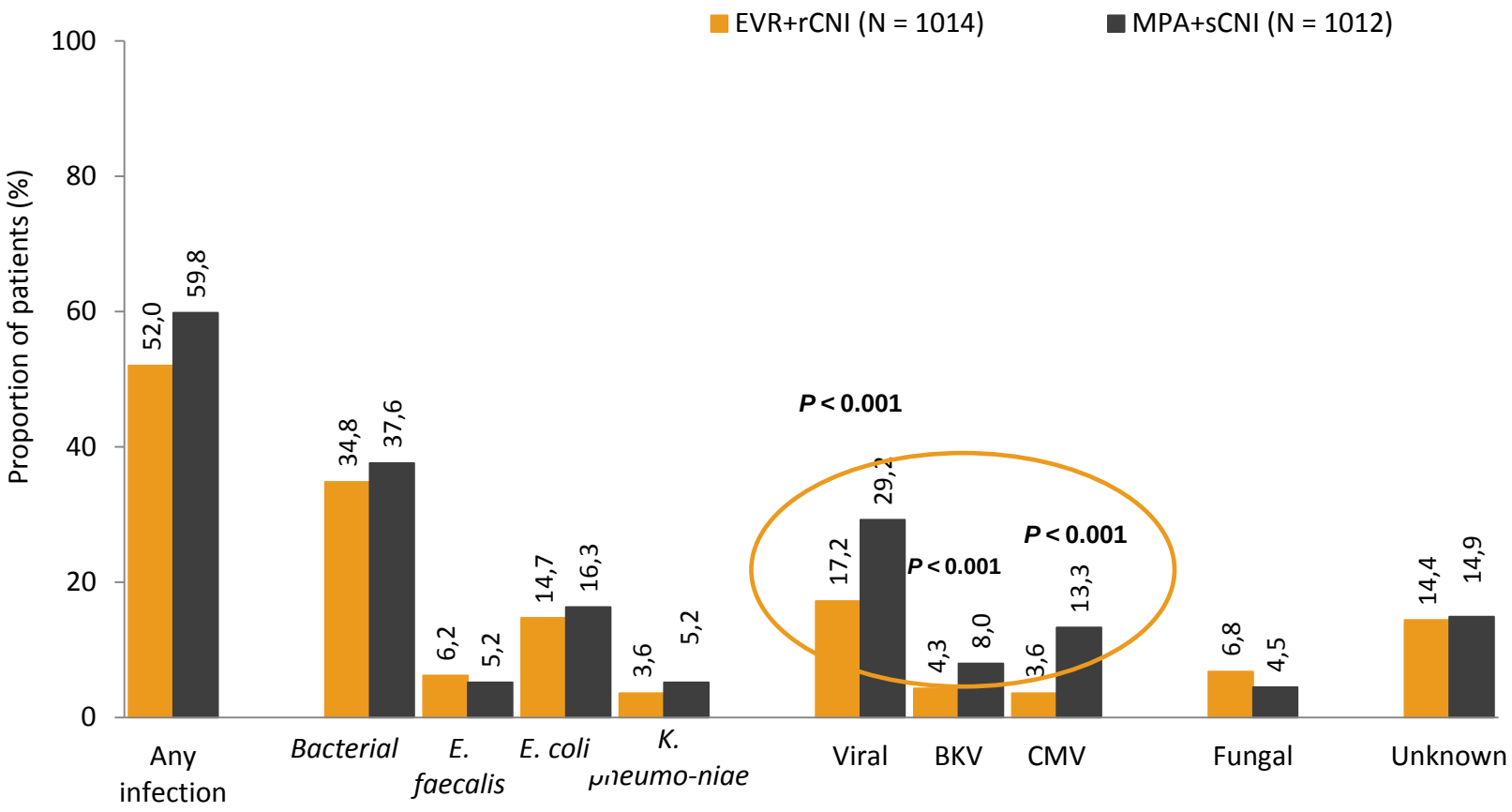
Safety analysis set – M12



Infections (≥5% in any group)

EVR+rCNI offers protection from viral infections

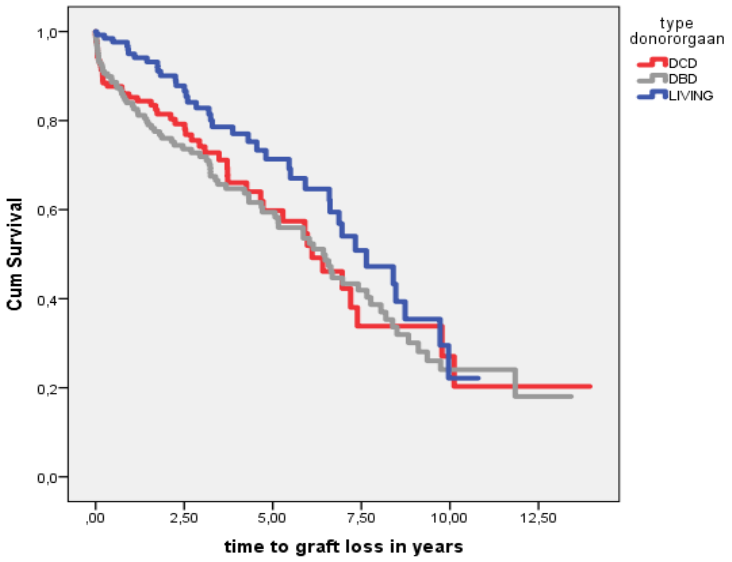
Safety analysis set – M12

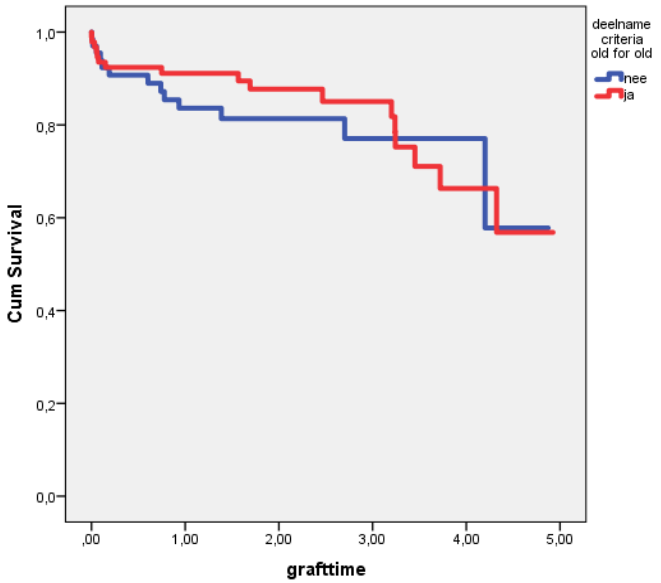


How do we measure outcome?

- Goal of transplantation is optimal graft en patient survival
- Rejection and renal function are surrogate markers
- None of the recent IS studies shows an effect on survival

Transplantsurvival in 65+ at UMCG 2014-2018





AMC
Erasmus MC
LUMC
RadboudUMC
UMCG
UMCU
UZ Leuven
VUMC

GGG Grote Trials

ZonMw

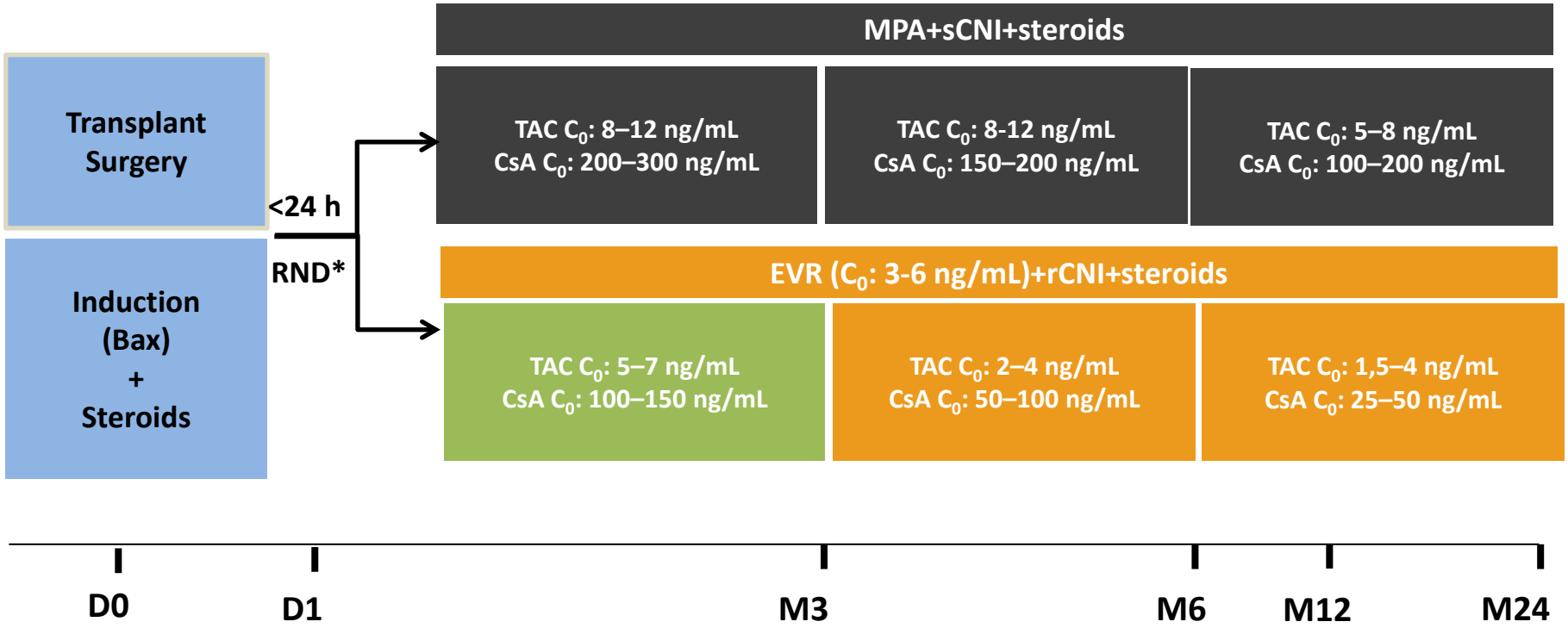
Principal Investigator: Stefan Berger
Project Leader: Jan-Stephan Sanders

OPTIMIZE

- **OP**en label multicenter randomized **T**rial comparing standard **IM**munosuppression with tacrolimus and mycophenolate mofetil with a low exposure tacrolimus regimen **I**n combination with everolimus in *de novo* renal transplantation in **E**lderly patients

PROTOCOL

- Stratum A: old-for-old
- Stratum B: older recipient of
  - Deceased donor < 65 years
  - Living donor



Immuunsuppressie, spiegels in ug/l:

Arm 1: Dag 0 en 4 Basiliximab 20 mg
TAC BL t/m M 6 visite: 8-12
TAC M 6 t/m M 24 visite: 5-8
MMF 2 x 500 mg
Prednisolon BL tot M 3: 20 mg, afbouwen naar
Prednisolon M 3 tot M 24: 5 mg.

Arm 2: Dag 0 en 4 Basiliximab 20 mg
TAC BL t/m M 3 visite: 5-7
TAC M 3 t/m M 6 visite: 2-4
TAC M 6 t/m M 24 vistie : 1.5-4
EVL vanaf BL t/m M 24 visite : 3-6
Prednisolon BL tot M 3: 20 mg, afbouwen naar
Prednisolon M 3 tot M 24: 5 mg.

Primary endpoint: succesfull transplantation

- Alive with functioning graft
- Kidney function
  - Stratum A -> 30 ml/min*1,73m2
  - Stratum B -> 45 ml/min*1,73m2

  - In stratum A, in each arm 96 patients
  - in stratum B in each arm 90 patients
  - in total **372** patients will be randomized

How do we improve outcome after kidney transplantation?

- Adapt immunosuppression to individual recipients
  - To improve adherence
  - Infection/malignancies
  - Elderly?

- Personalized medicine should be our goal in transplantation

Thank you for your attention!