

Complicaties na levertransplantatie

Sarwa Darwish Murad
MDL arts
Erasmus MC

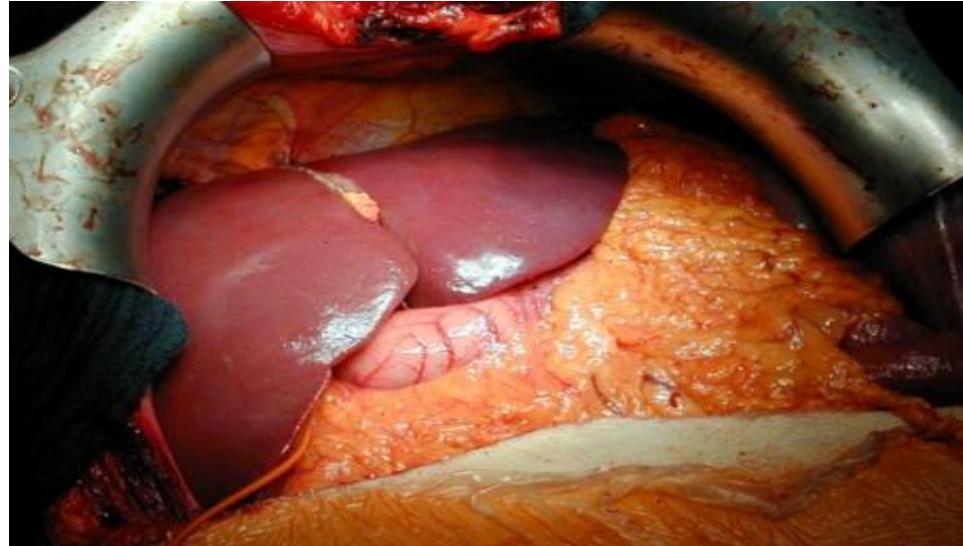
Dutch Liver Week 2018

Donor populatie

Complicaties, transplantatie gerelateerd

Complicaties, immuunsuppressie gerelateerd

Complicaties, overig



DONOR POPULATIE ANNO NU

De ideale donor ...



Erasmus MC
Zapfus

De realiteit ...



Percentage volwassenen met overgewicht en obesitas van 1981-2015

20 jaar en ouder

Percentage

60

40

20

0

1985 1990 1995 2000 2005 2010 2015

— Totaal overgewicht, man — Totaal overgewicht, vrouw -·- Aandeel obesitas, man
-·- Aandeel obesitas, vrouw

Toename donor leeftijd

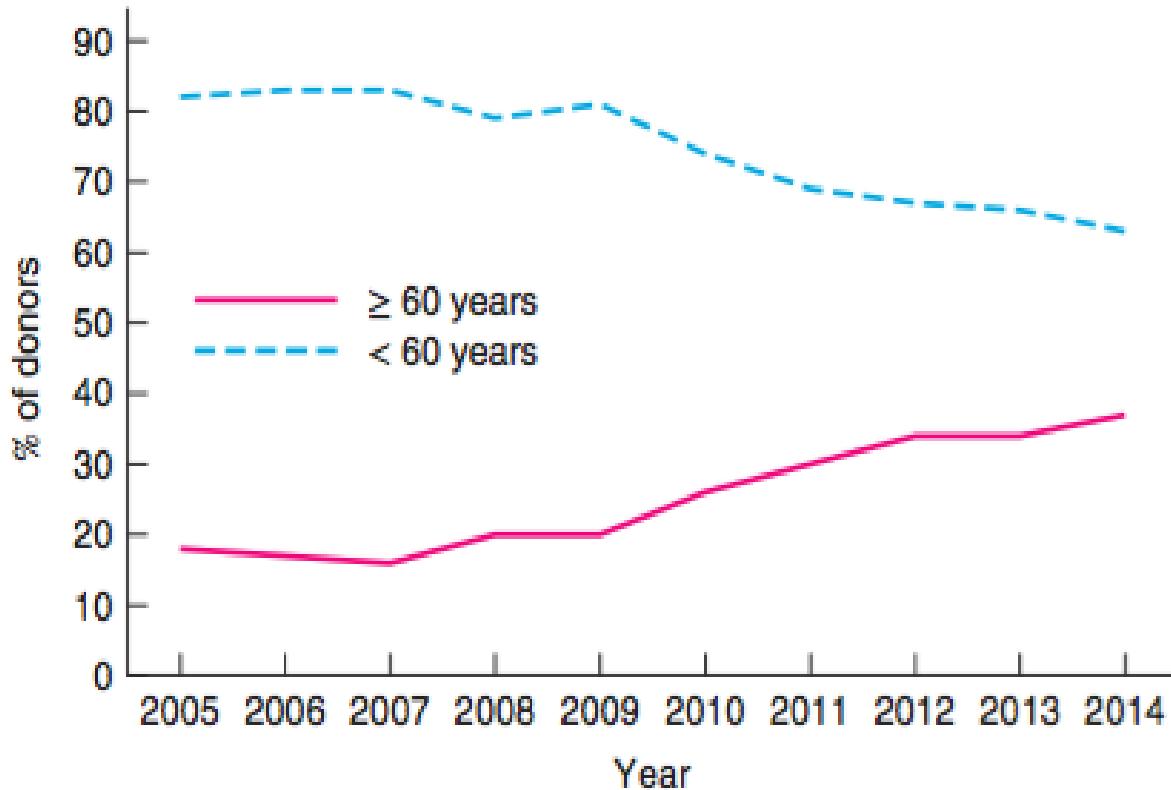
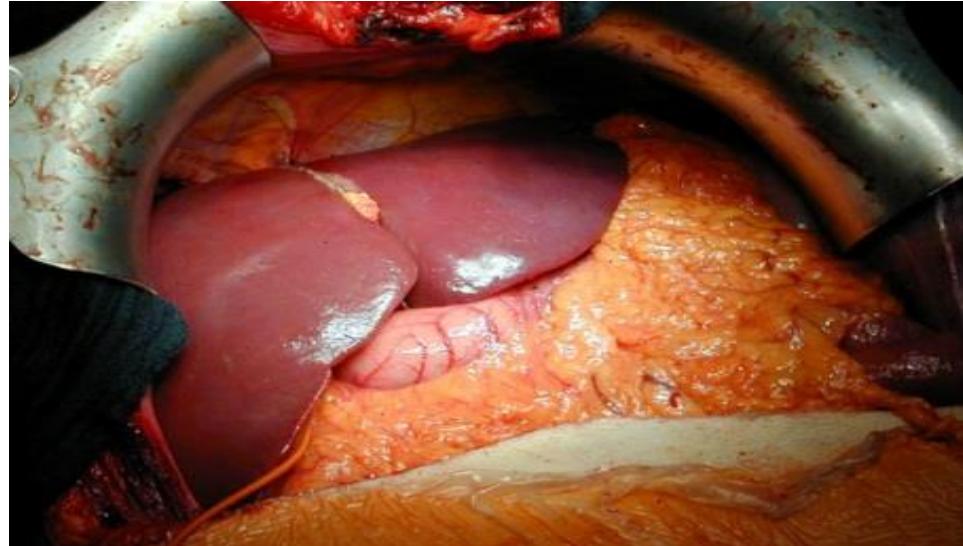


Fig. 1 Percentage of deceased donors aged at least 60 years in the UK (National Health Service Blood and Transplant⁸)



COMPLICATIES TRANSPLANTATIE GERELATEERD

Primary non-function Early allograft dysfunction

PNF:

ASAT > 10.000 U/L en/of INR > 3.0 en/of lactaat > 3 mmol/L en/of geen gal productie

Incidentie: 6%

Indicatie high urgency re-LTx

EAD:

Bilirubine \geq 170 $\mu\text{mol/l}$ op dag 7

INR \geq 1.6 op dag 7

ASAT of ALAT > 2000 U/L in 1^e wk



Incidentie: 23%

Risicofactor mortaliteit (RR 10.7) en graft loss (RR 7.4)

Vasculaire complicaties

- Vroege arteria hepatica trombose (<1m)
5-10%
- Late HAT
1-5%
- Vena portae trombose /stenose
3%
- Stenose piggyback cavo-cavostomie (secundaire Budd-Chiari)
<1%



Behandeling

- Retransplantatie (vroege HAT of galwegschade bij late HAT)
- Radiologische angioplastiek / stent
- (chirurgische revisie)
- Antistolling

Galwegcomplicaties

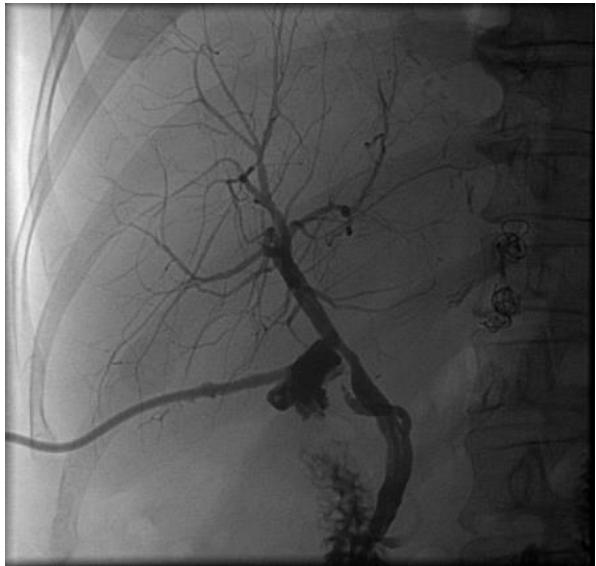
Combinatie techniek + ischemie

- Stenose galweg anastomose 9-12%
- Gallekkage +/- biloom 2-21%
- Niet-anastomotische stricturen (NAS) 10-15%

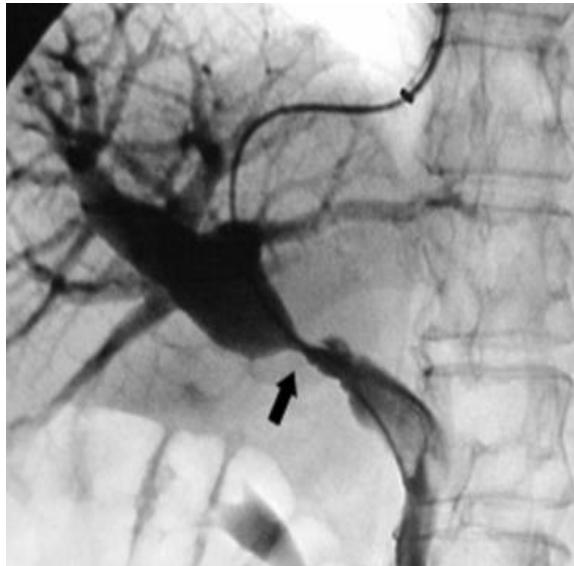
Behandeling

- ERCP of PTC of drainage (biloom)
- Vaak herhaaldelijk (20% recurrent)
- Hepaticojejunostomie +/- revisie
- Retransplantatie (tot 50%)

Gallekkage



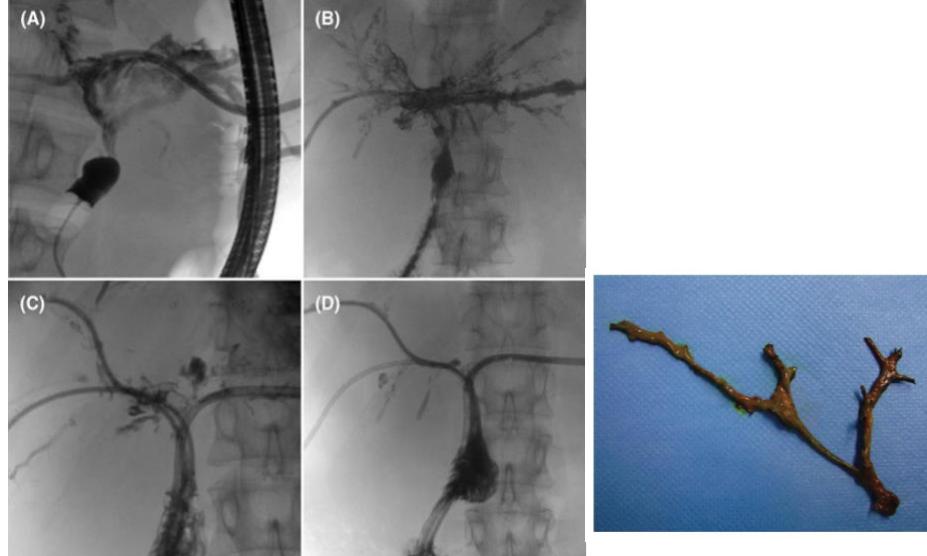
Stenose anastomose



Stenose HJ

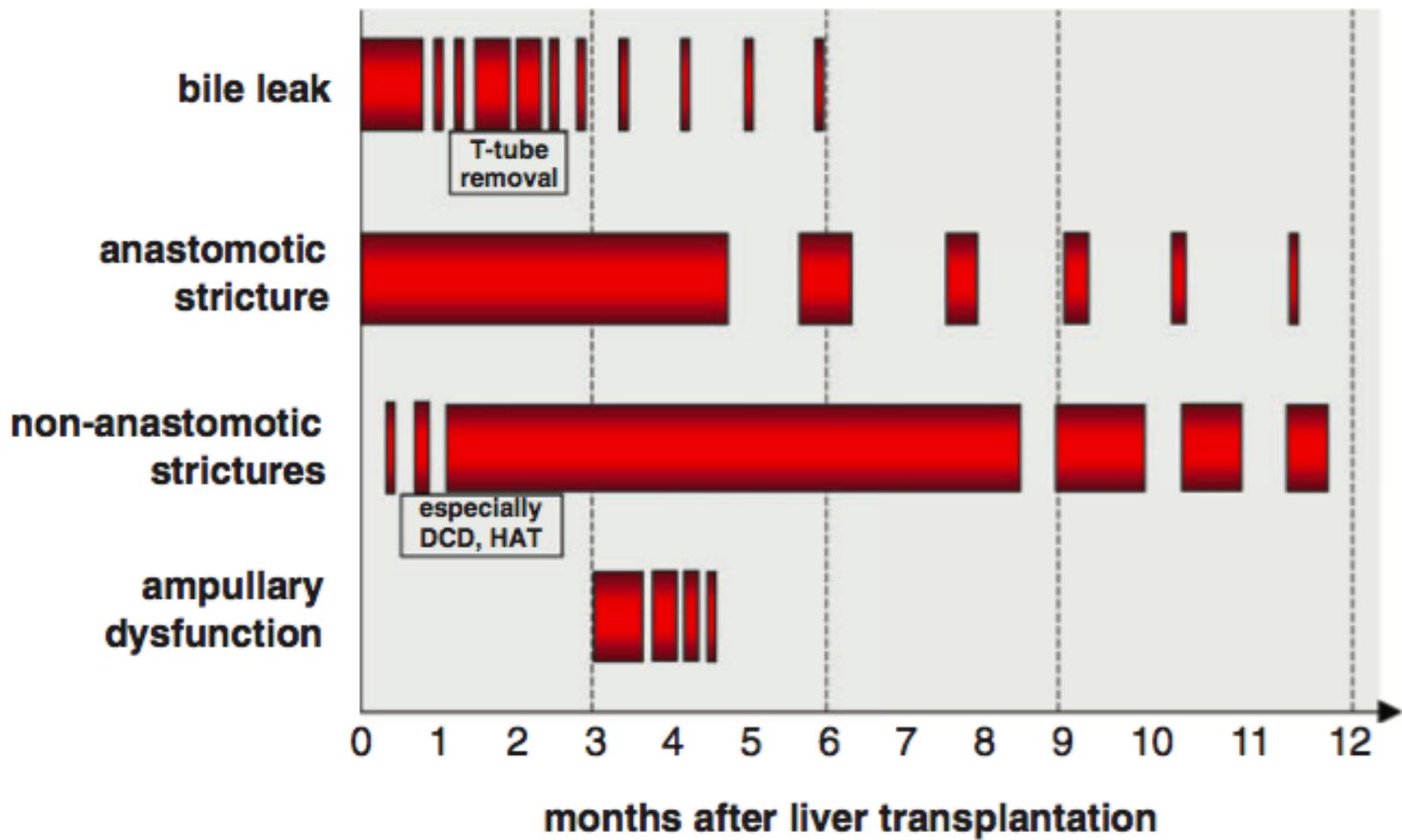


Ischaemic type biliary lesions (ITBL)



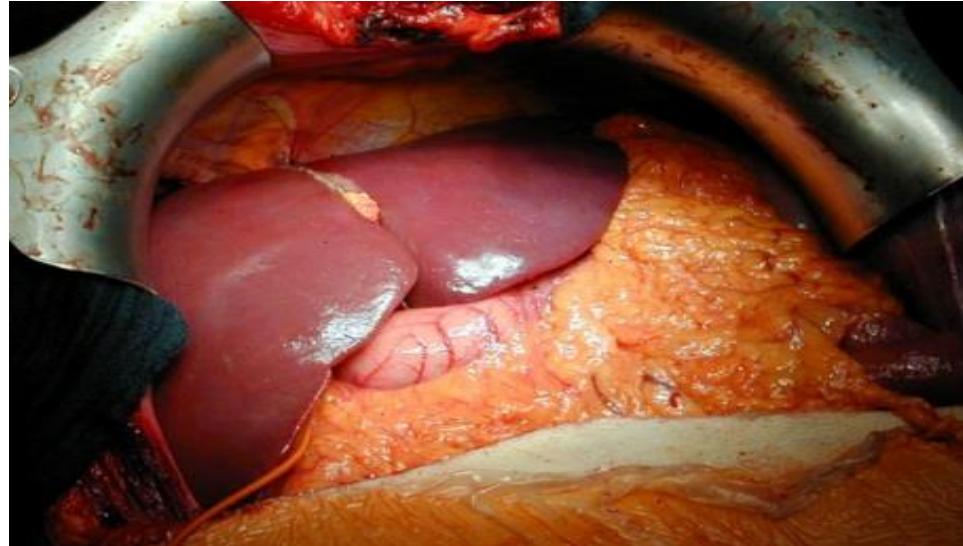
Galwegcomplicaties in de tijd

Seehofer et al.



Complicaties na DCD LTx

	DCD (n=55)	DBD (n=471)	P-value
Primary Non-Function	1 (2%)	7 (2%)	0.84
Biliary leakage	2 (4%)	2 (0.4%)	0.42
Non-Anastomotic Biliary Strictures	13 (24%)	37 (8%)	<0.001
HAT	4 (7%)	22 (5%)	0.44



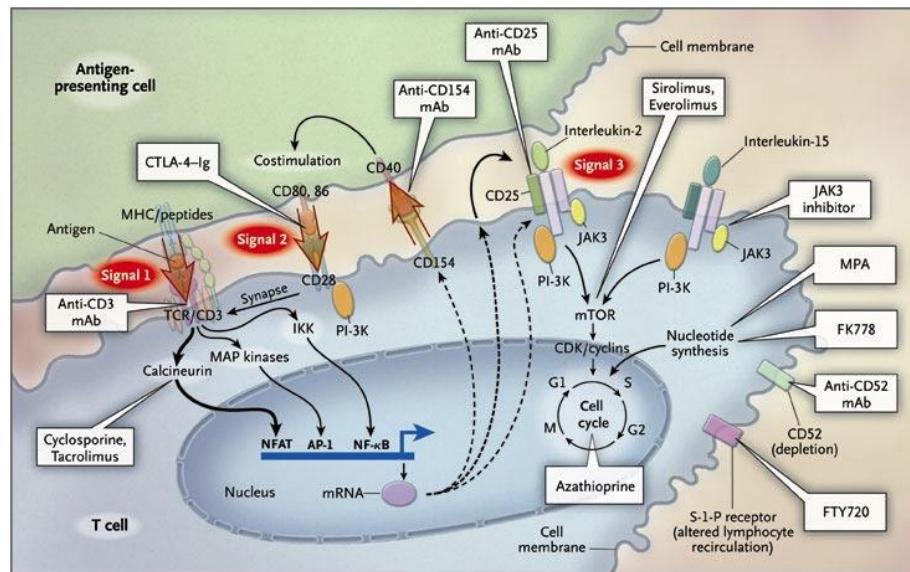
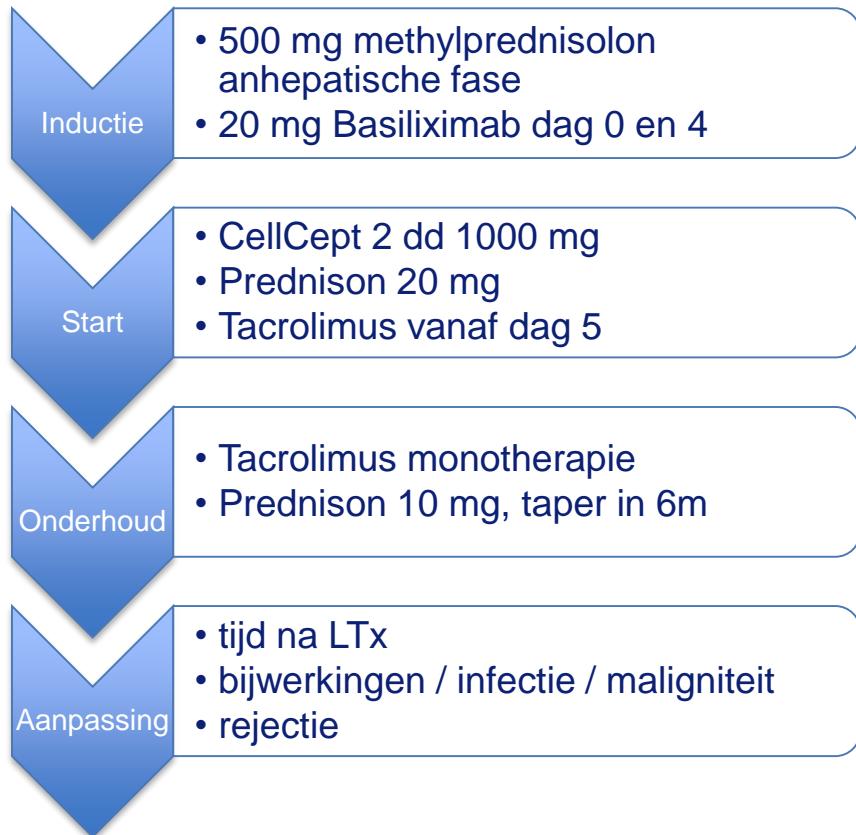
COMPLICATIES IMMUUNSUPPRESSIE GERELATEERD

Rejectie

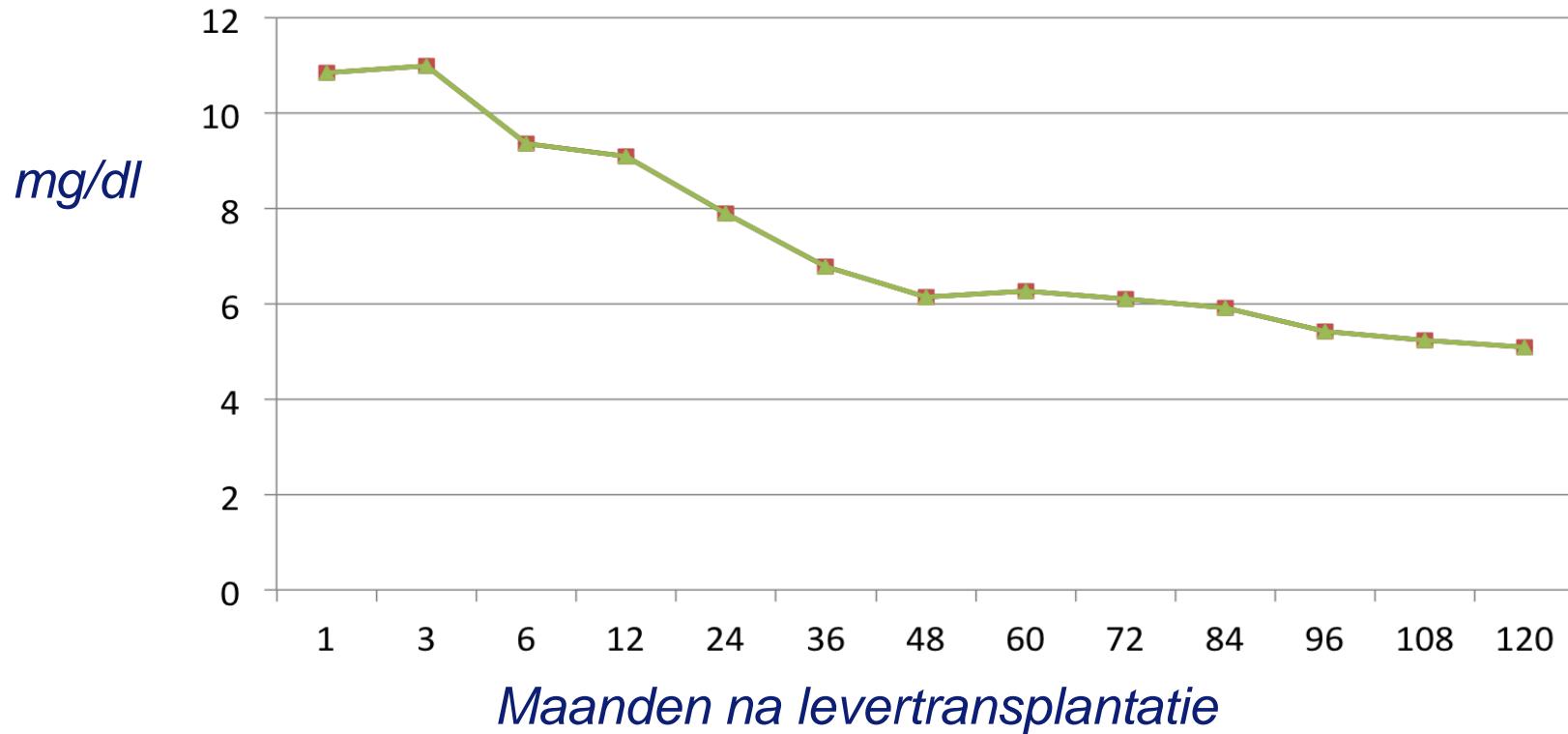


"I'M AFRAID YOUR BODY IS REJECTING THE TRANSPLANT..."

Standaard immunosuppressie



Tacrolimus dalspiegel in tijd



TARGET

week 0-6 6-10 mg/dl

week >6 4-8 mg/dl

Rodriguez-Peralvarez et al. Am J Transplant 2012; Neuberger et al. Tramsplantation 2017

Type rejectie

Acute cellulaire rejectie

- Vroeg (< 3m) AF/GGT
portale ontsteking, endothelitis, cholangitis
- Laat ASAT/ALAT
centrale perivenulitis

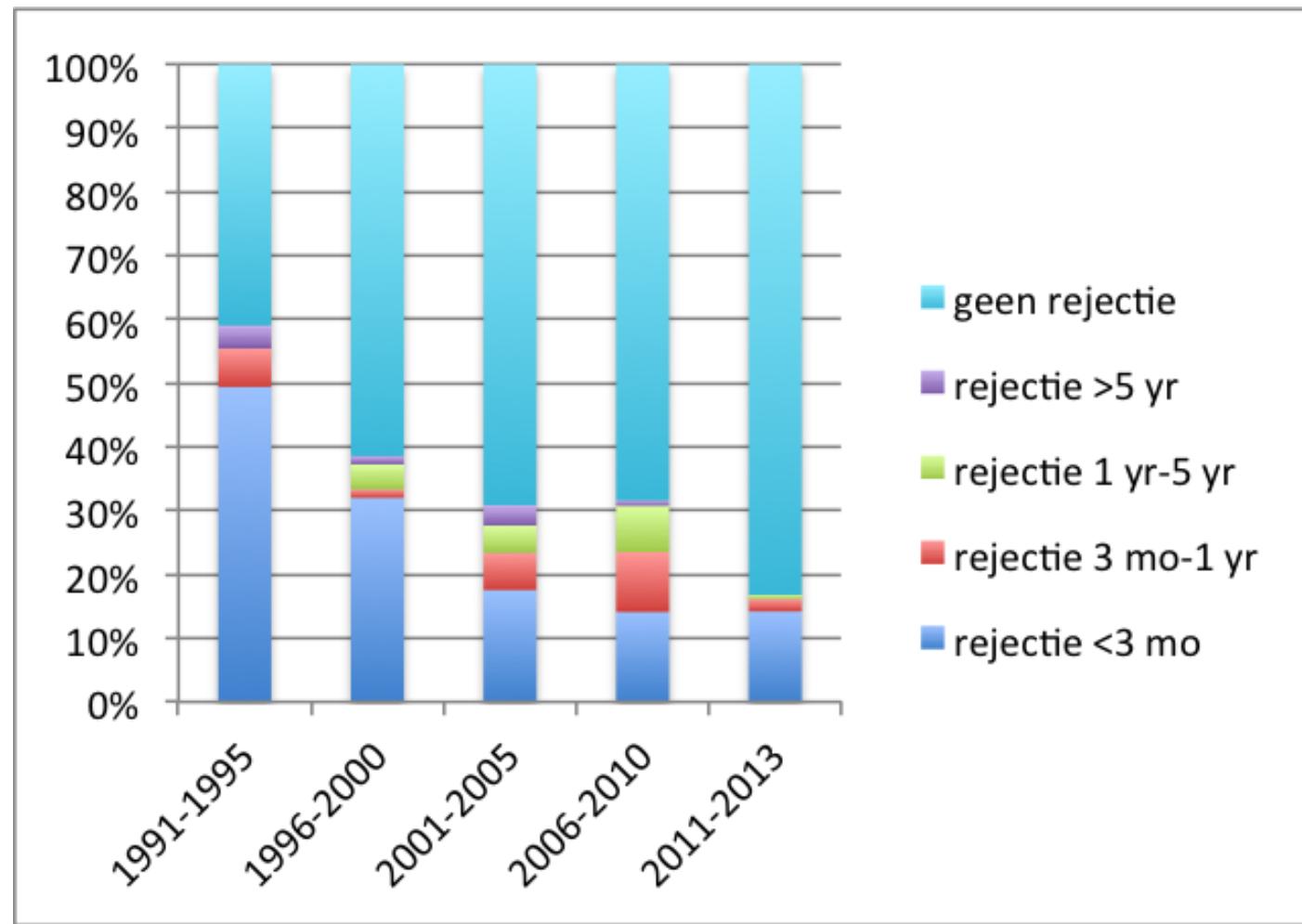
Chronische cellulaire rejectie

- Kan al > 6 mnd
- Bilirubine, AF/GGT
- Ductopenie, obliteratieve arteriopathie

Humorale rejectie

- Donor-specifieke antistoffen ; onder-immuunsuppressie
- ASAT/ALAT, allograft dysfunctie
- CD4 kleuring

Afname aantal behandelde acute afstotingen



Infectie

© Mike Baldwin / Cornered

Baldwin



“The patient in the next bed is highly infectious. Thank God for these curtains.”

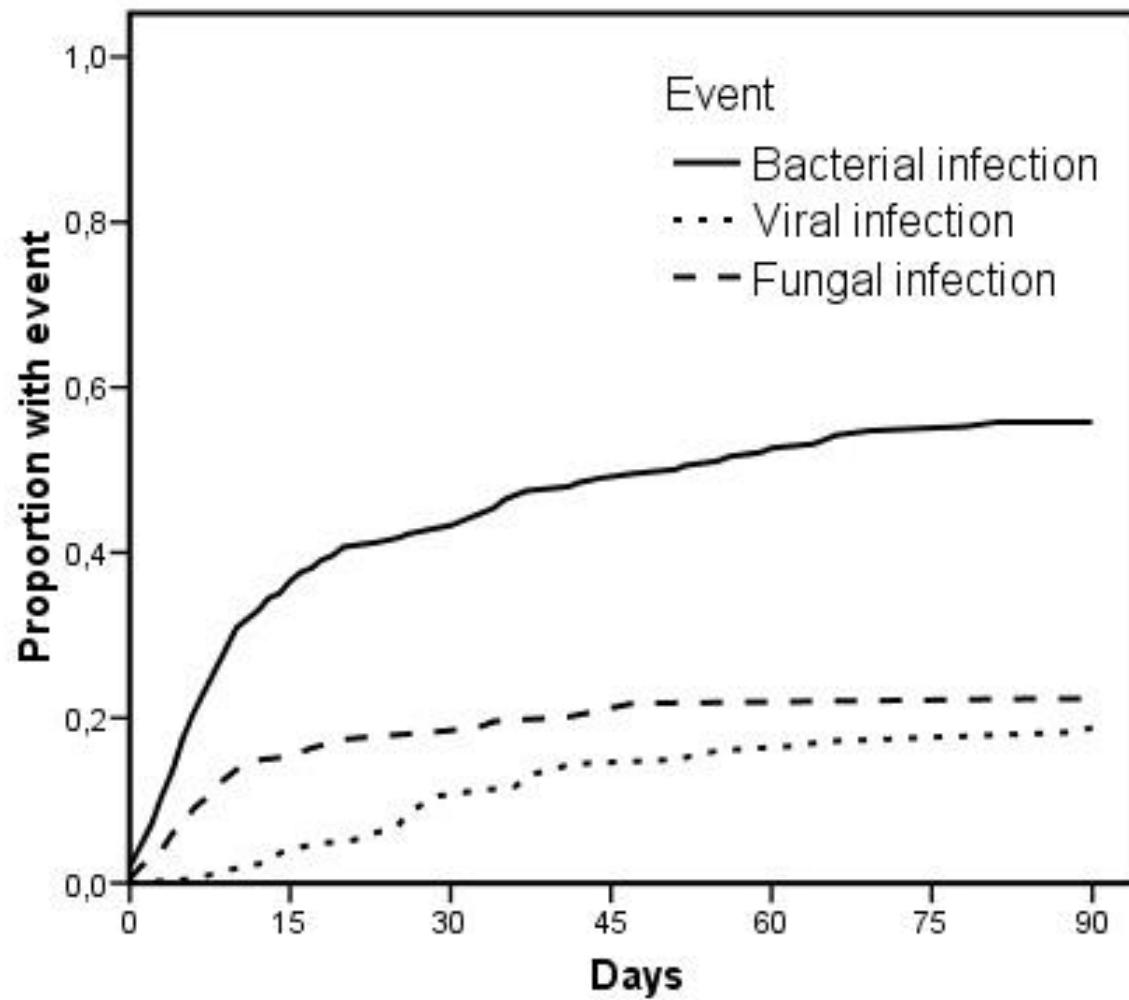


Uw patiënt is nu 3 maanden na LTx en ontwikkelt koorts.

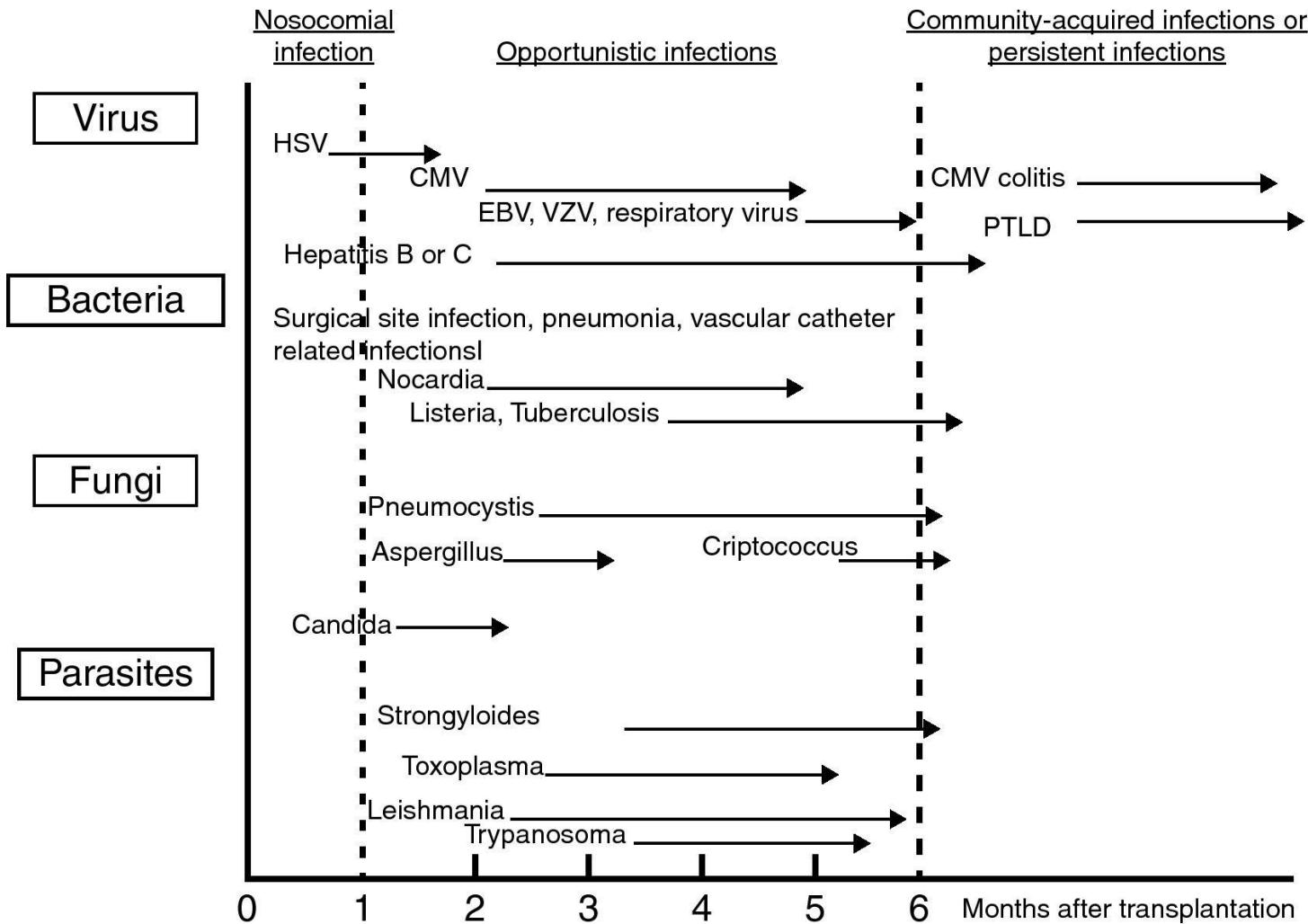
Waar denkt u in eerste instantie niet aan?

1. opportunistische schimmel infecties
2. virale verwekkers
3. EBV gerelateerd lymfoom (PTLD)
4. urine weg infectie

Infecties na levertransplantatie



Infecties na orgaantransplantatie

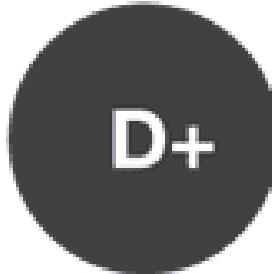


CMV infectie

Donor organ
does not
have CMV



Donor organ
has CMV



Recipient does
not have CMV



Recipient
has CMV



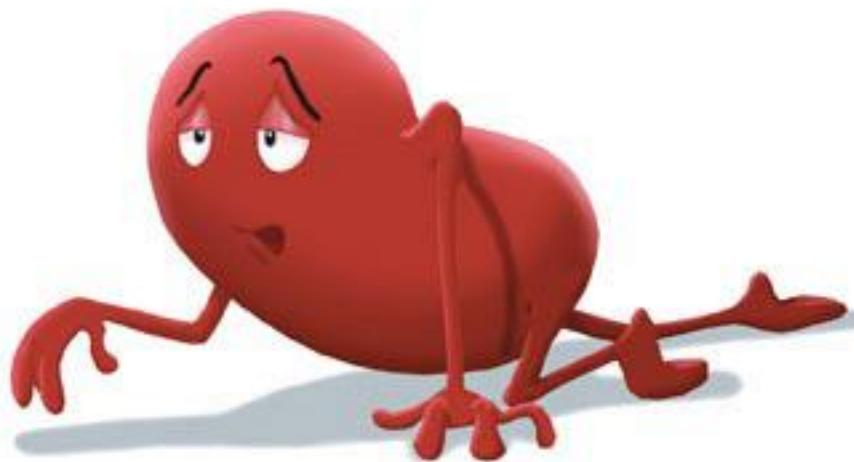
Primo

Reactivatie

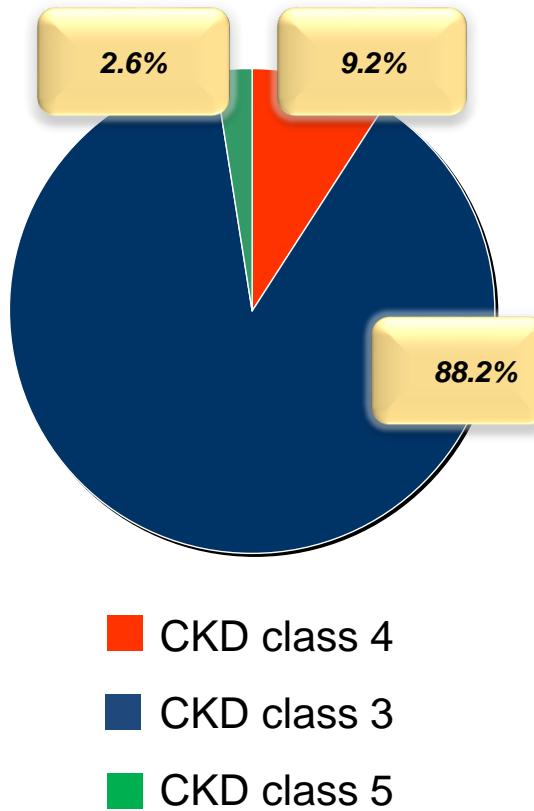
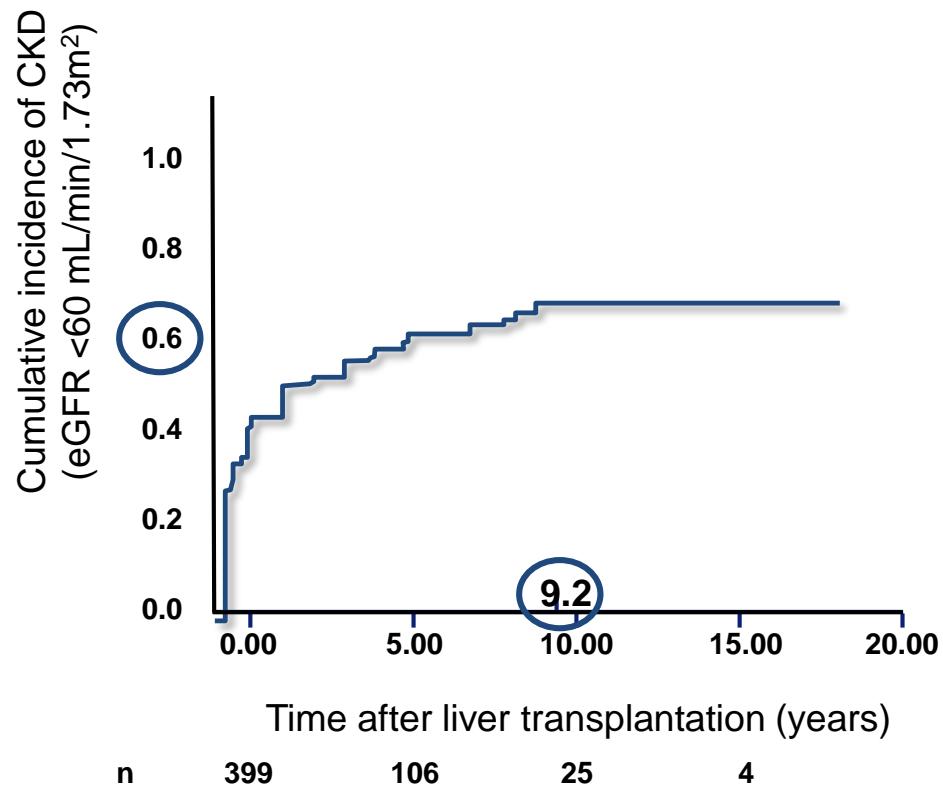
Valgancylovir

- Preventief bij mismatch (3m)
- Therapeutisch bij infectie

Chronische nier insufficiëntie



Chronische nierziekte na LTx



Nierfalen meest frequent na LTx

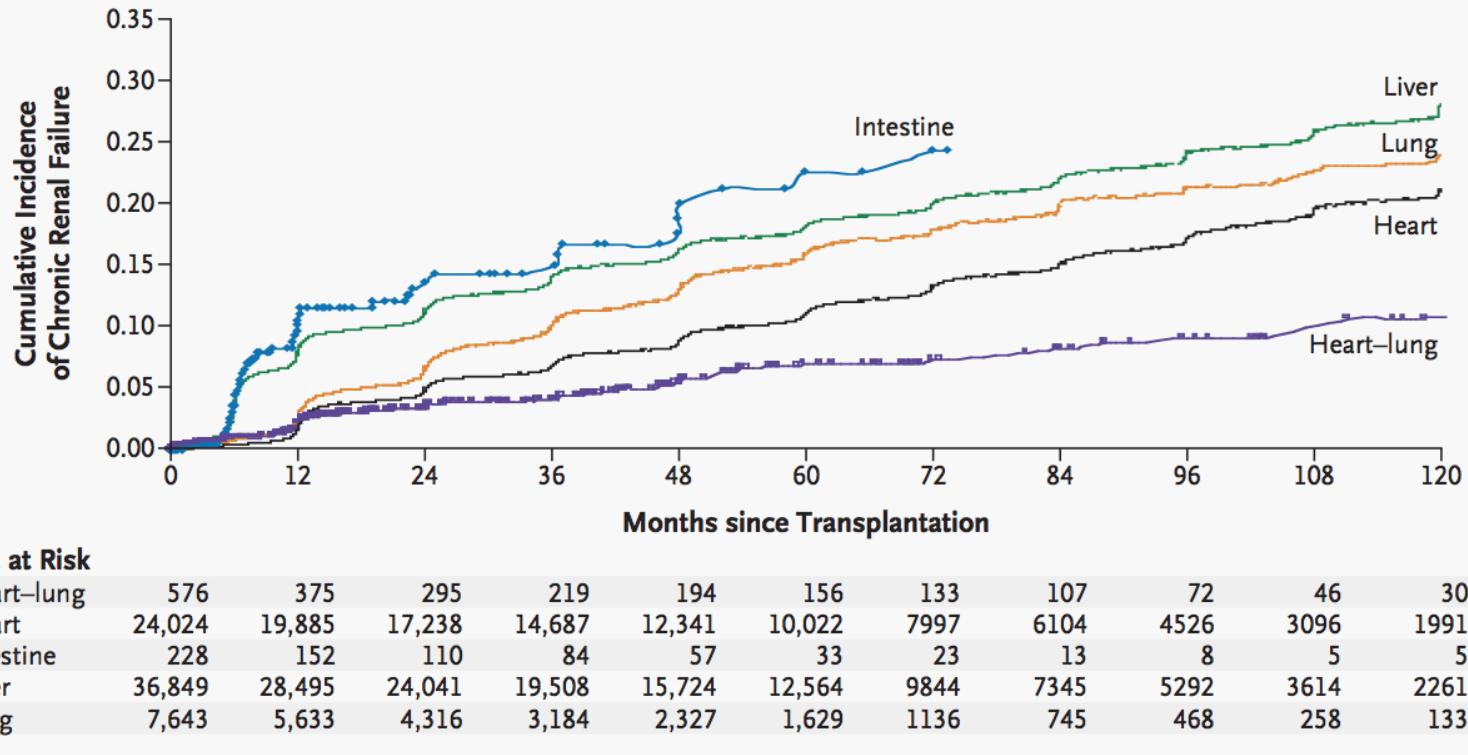


Figure 1. Cumulative Incidence of Chronic Renal Failure among 69,321 Persons Who Received Nonrenal Organ Transplants in the United States between January 1, 1990, and December 31, 2000.

The risk of chronic renal failure was estimated with a noncompeting-risk model. Measurements of renal function were obtained at six-month intervals during the first year and annually thereafter.

Nierfalen - risico en behandeling

Risicofactoren

Leeftijd, vrouw, HCV, hypertensie, DM, post-operatief AKI

Pre-LTx HRS

CNI (Tacrolimus / Cyclosporine; >50%)

Vaker na introductie MELD systeem

Tevens toename gecombineerde lever-nierTx

Behandeling

Grootste kans van slagen indien vroeg (eGFR>60 ml/min)

Dosisverlaging Tacrolimus, additie MMF / sirolimus of Everolimus - MMF

Metabole effecten immuunsuppressie





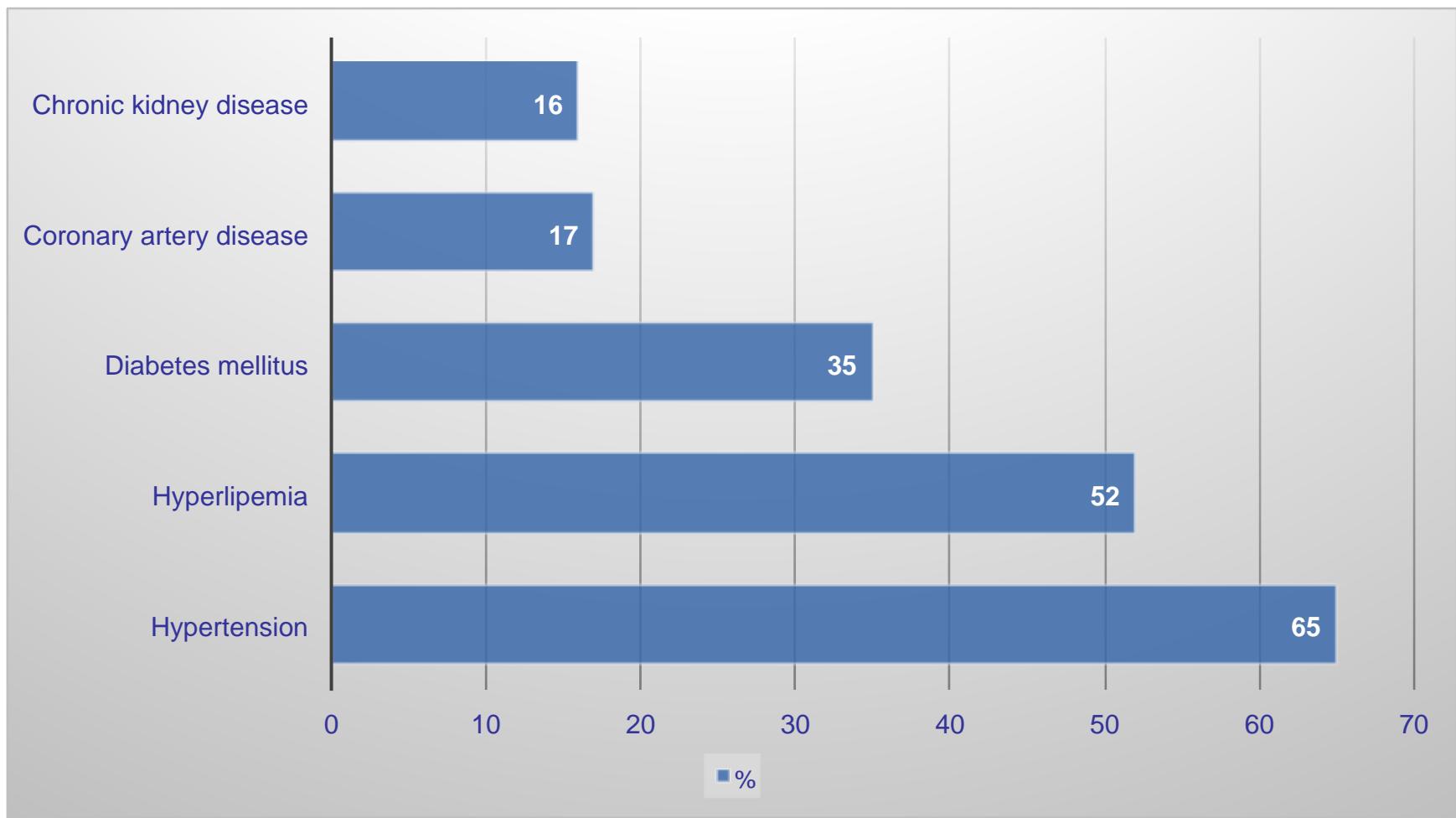
De meest voorkomende metabole complicatie na LTx is

1. Diabetes mellitus
2. Hyperlipidemie
3. Overgewicht
4. Hypertensie

Bijwerkingen immuunsuppressie

Adverse effect	Tacro	MMF	mTOR	Steroids
Diabetes	++	-	+	+++
Hypertension	++	-	++	+++
Hyperlipidemia	+	-	+++	++
CKD	+++	-	+	-
Osteoporosis	+	-	-	+++
BM suppression	-	++	+	-
Dermatologic	++	-	+	+
Neurotoxicity	++	+	+	+
GI toxicity	+	+++	++	+

Meest voorkomende metabole complicaties



LTx onafhankelijke RF cardiovasculaire events

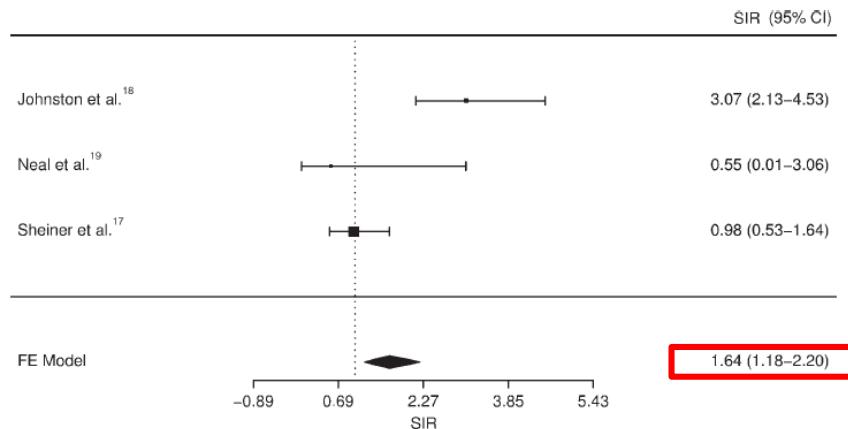
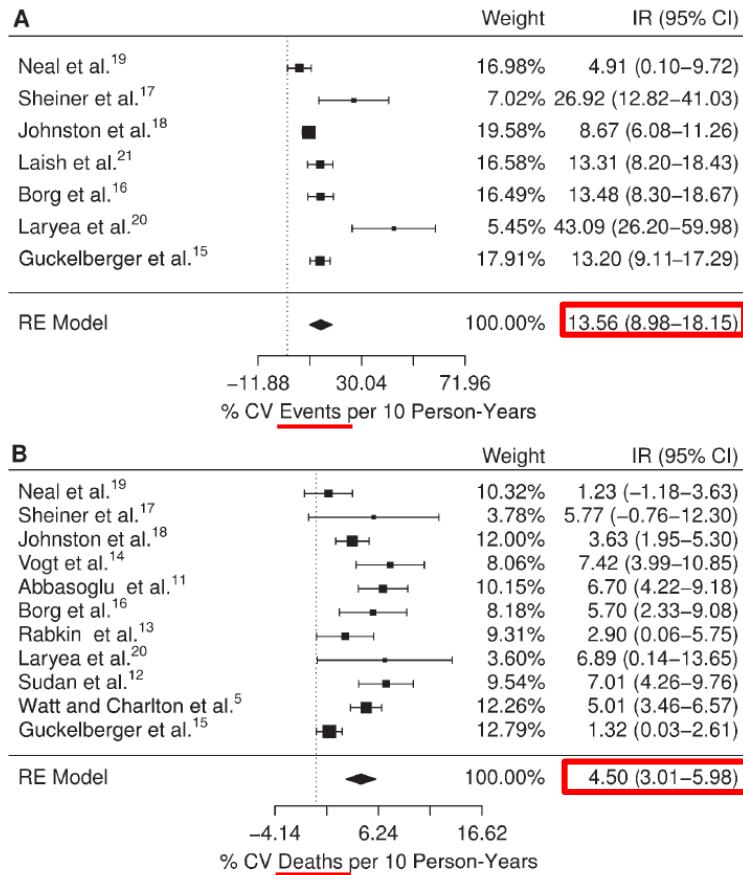
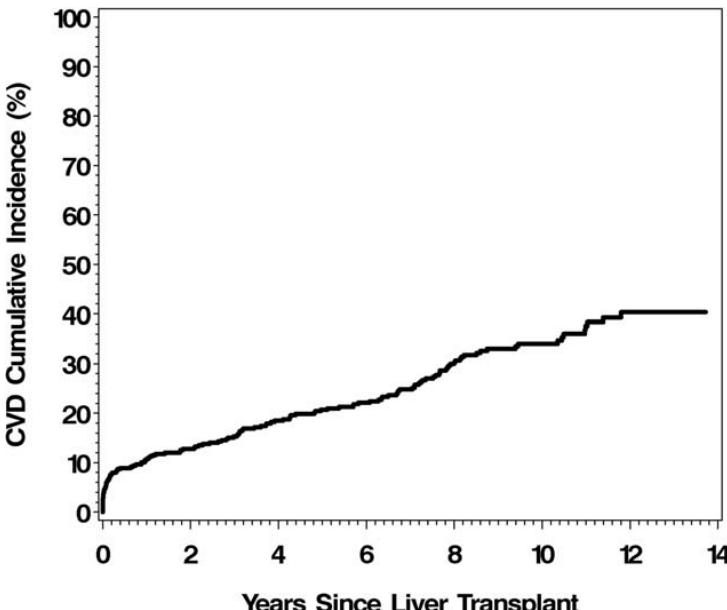


Figure 3. Pooled estimates of SIRs for liver transplant recipients versus the general population.



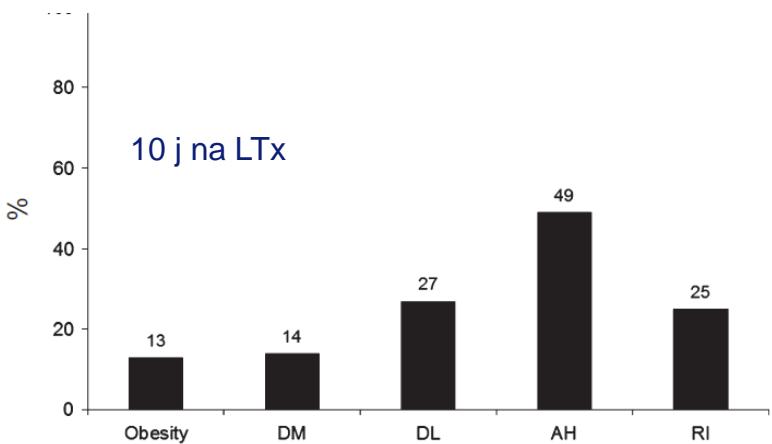
Metabool syndroom

Meeste gewichtstoename in 1^e j

67% verhoogt calorie inname

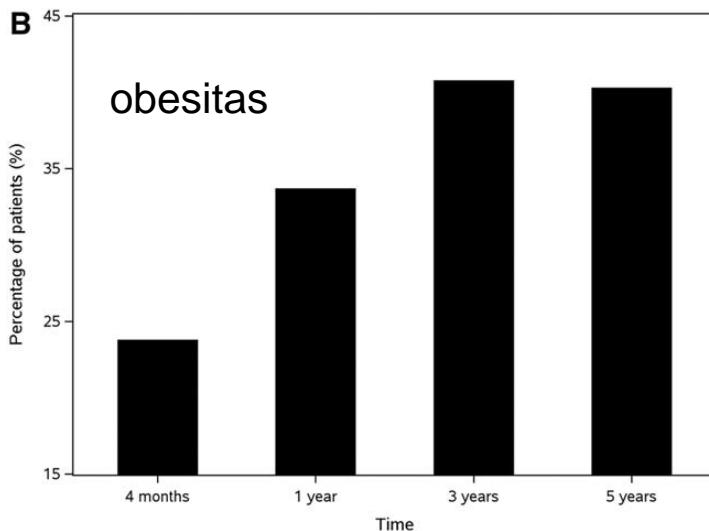
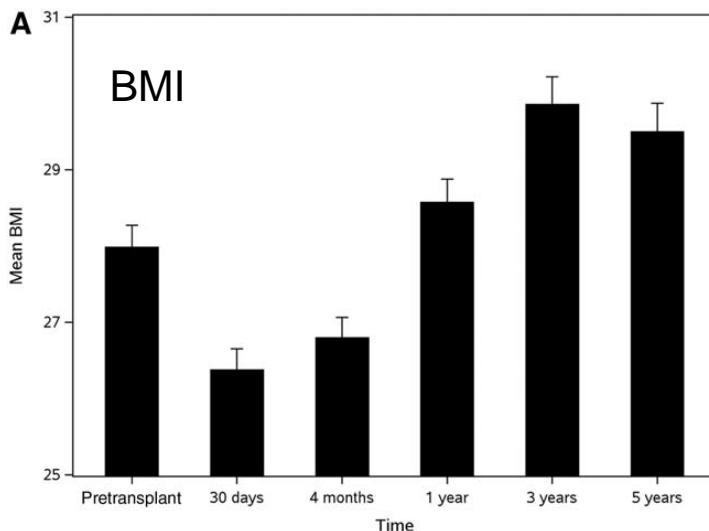
Slechts 25% fysiek actief

Risico metabool syndroom blijft toenemen



DM = Diabetes mellitus; DL = Dyslipidemia; AH = arterial hypertension;

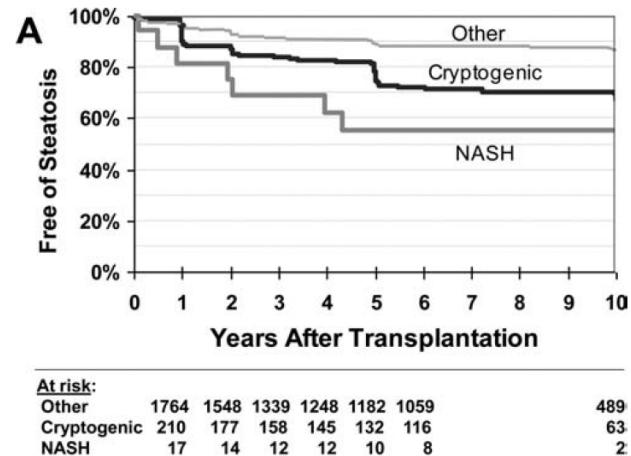
RI = renal insufficiency



Czafus

De novo en recurrent NAFLD

	Recurrence	De novo
NAFLD	30-60%	18-31%
NASH	10-33%	5-9%
NASH + gevorderde fibrose	5-10%	0-4%



Natuurlijk beloop versneld in rNAFLD

Metabole risicofactoren + Tacrolimus / steroiden
→ stapsgewijze toename risico

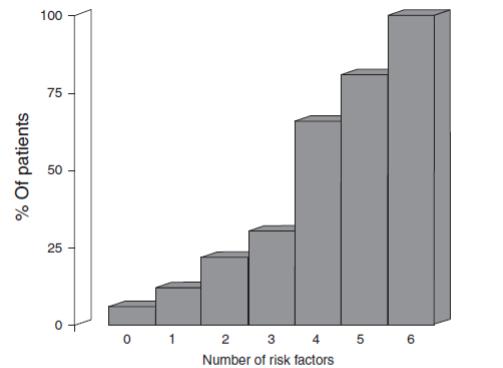
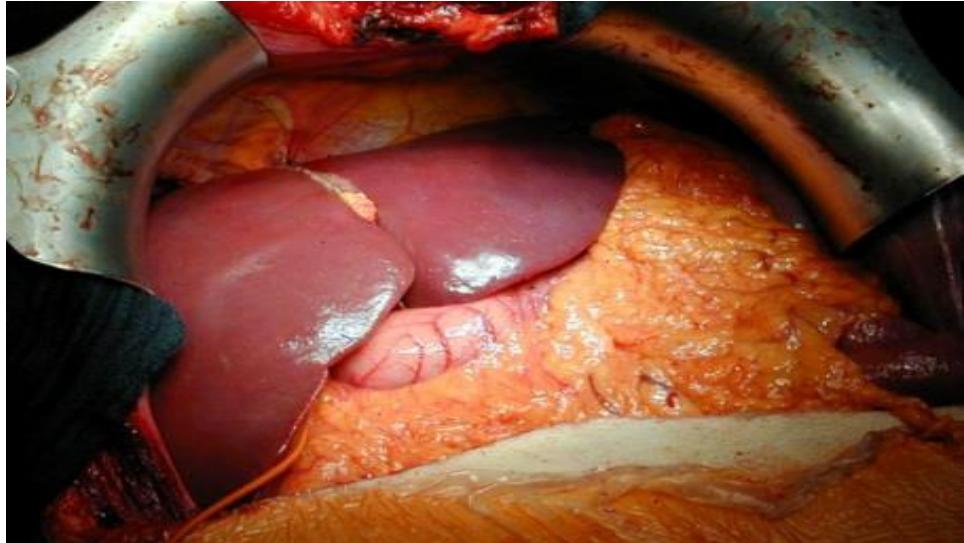


Figure 2. Relationship between the number of risk factors (obesity at the time of liver biopsy, tacrolimus-based regimen, diabetes mellitus, hyperlipidemia, arterial hypertension, alcoholic cirrhosis as primary indication for LT, and liver graft steatosis) and the risk of non-alcoholic fatty liver disease after liver transplantation (LT).

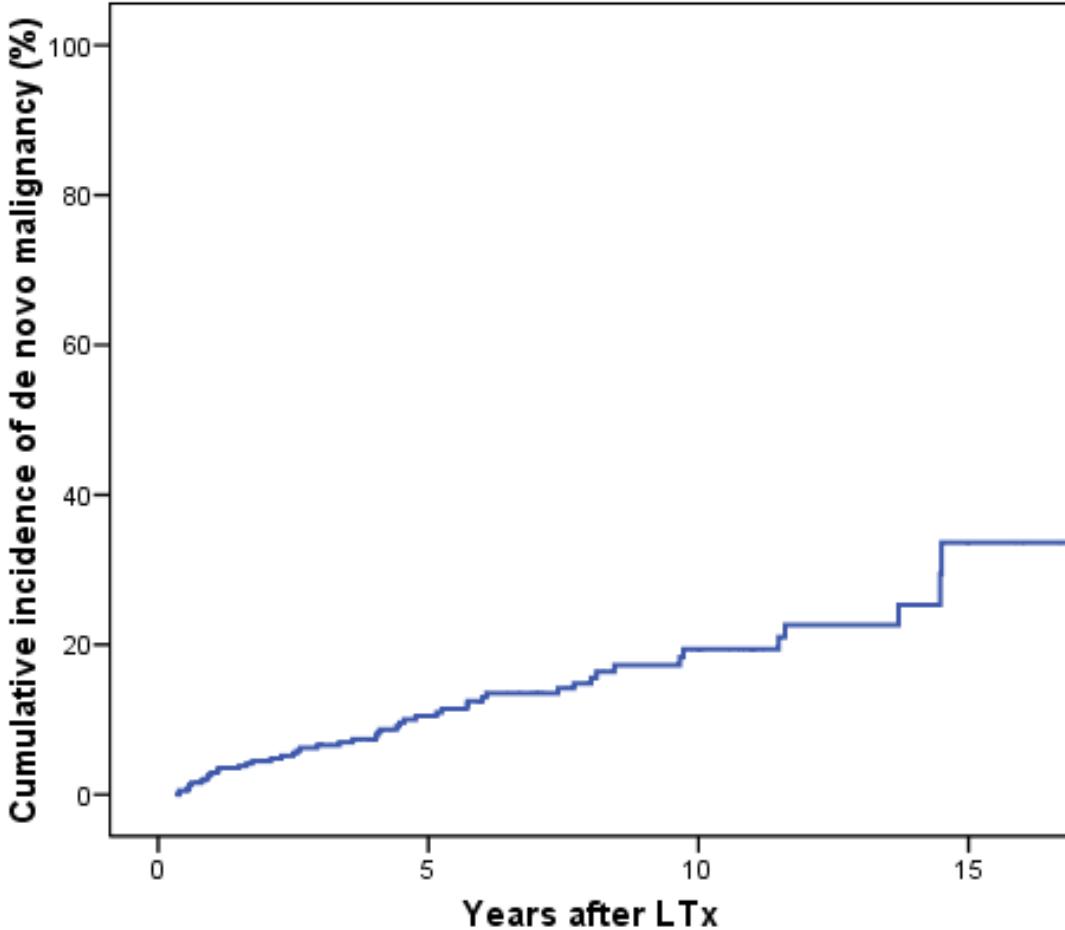




COMPLICATIES

OVERIG

Maligniteit na LTx



Aantal patiënten

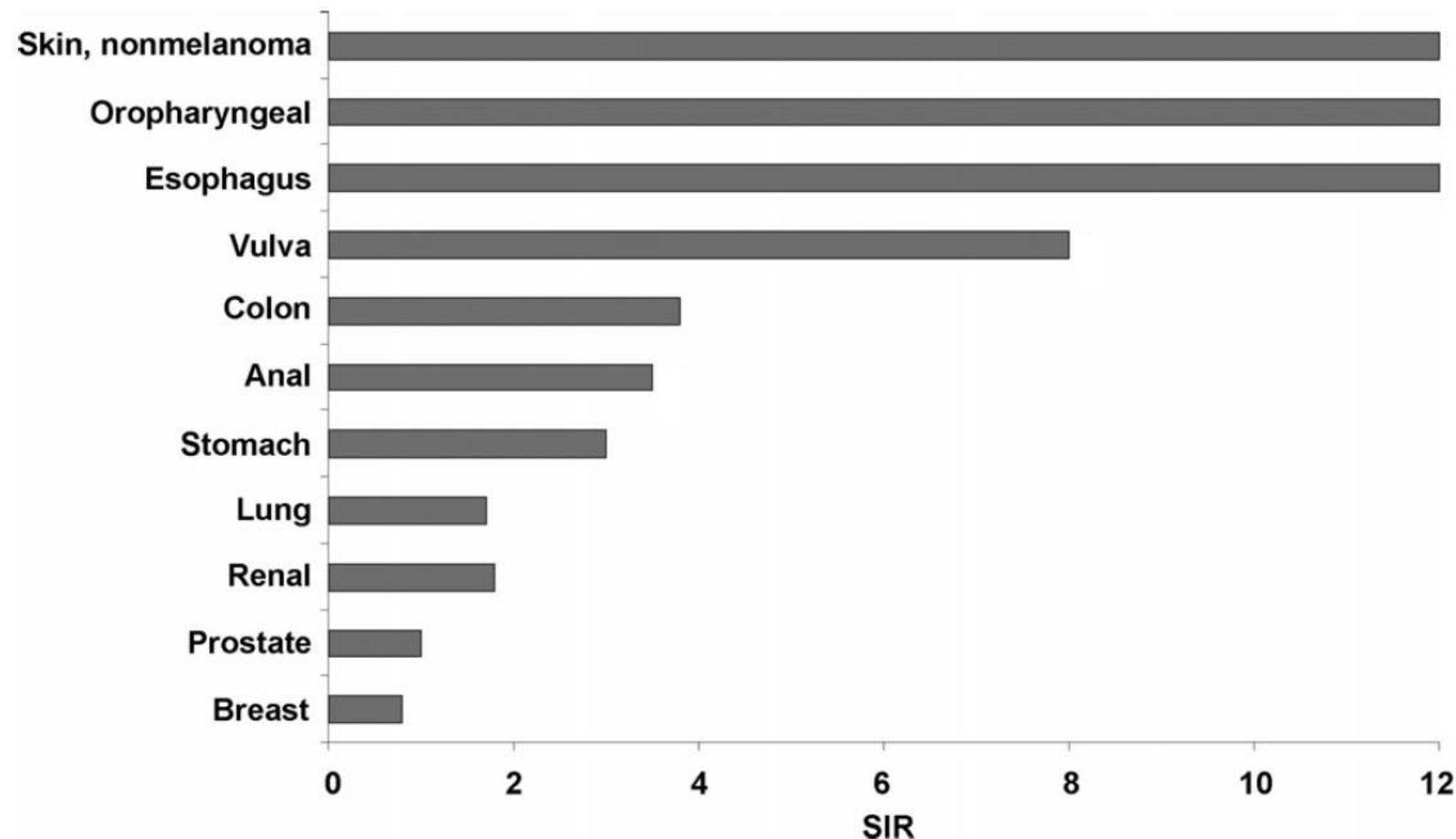
At risk: 385

Kanker: 50 (13.0%)

	Cum. Risico (%)	95% CI (%)
1 jaar	2.9	2.0 - 3.8
5 jaren	10.5	8.7 – 12.3
10 jaren	19.4	16.4 – 22.4
15 jaren	33.6	26.8 – 40.4

SIR= 2.2 (95% CI 1.6-2.8)

Incidentie t.o.v. algemene populatie



Post-transplantatie lymfoproliferatieve ziekte (PTLD)

- SIR lymfoom na LTx 7.7
- Vaker bij kinderen + jong volwassenen
- EBV infectie : RR 70

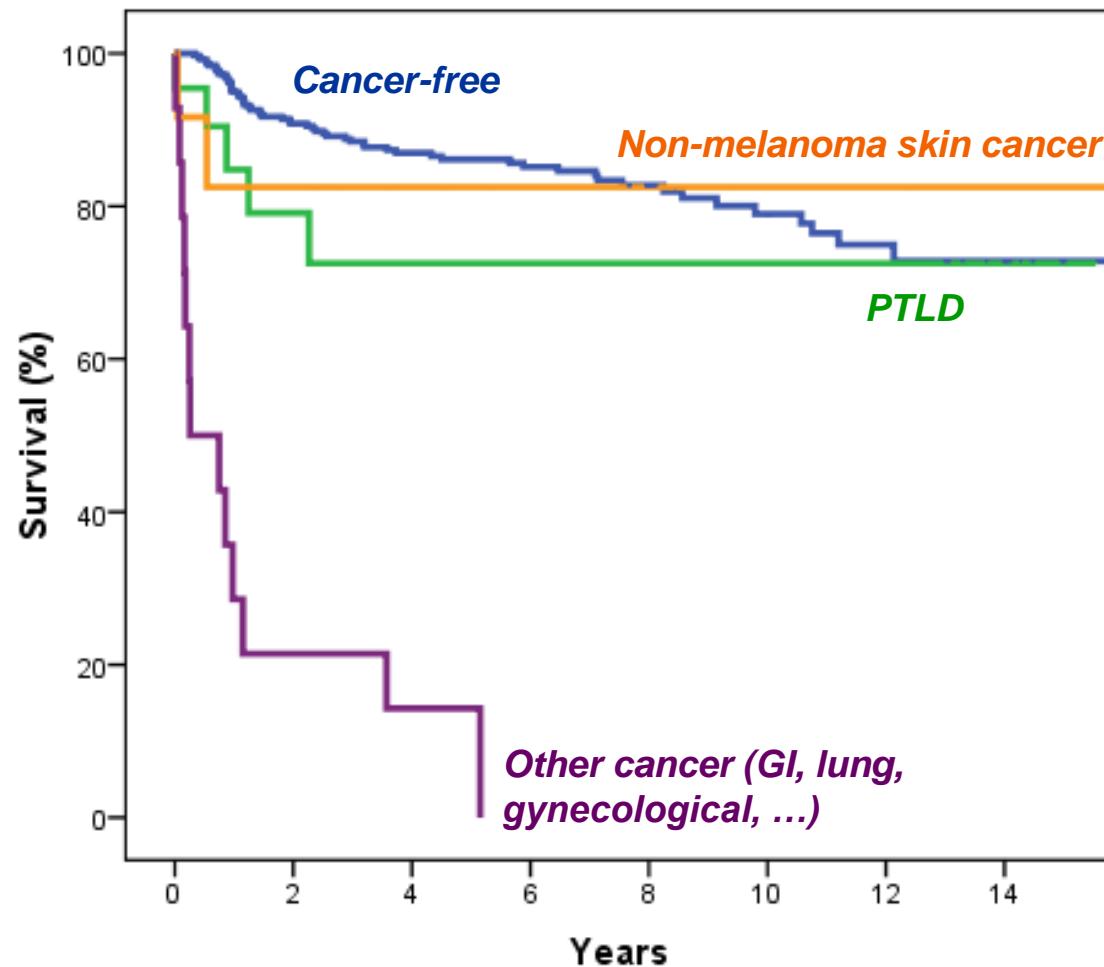
- Mononucleosis (polyclonaal) →→hooggradig lymfoom (85% Bcell)

- Non-EBV gerelateerde PTLD : slechtere prognose (monoclonaal; Tcell)

Behandeling

- Reductie immuunsuppressie (45-70% succes)
- Rituximab (44-65% succes)
- Systemische chemo (CHOP)

Effect van *de novo* kanker op overleving

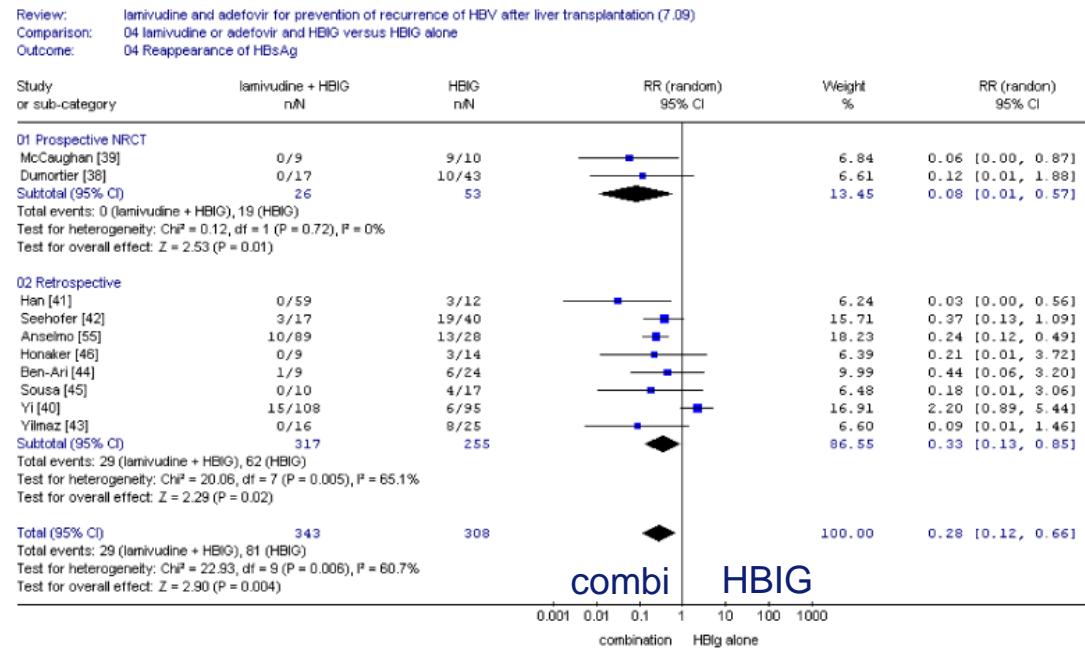


Terugkeer virale hepatitis

Universeel bij actieve infectie

HBV recurrence

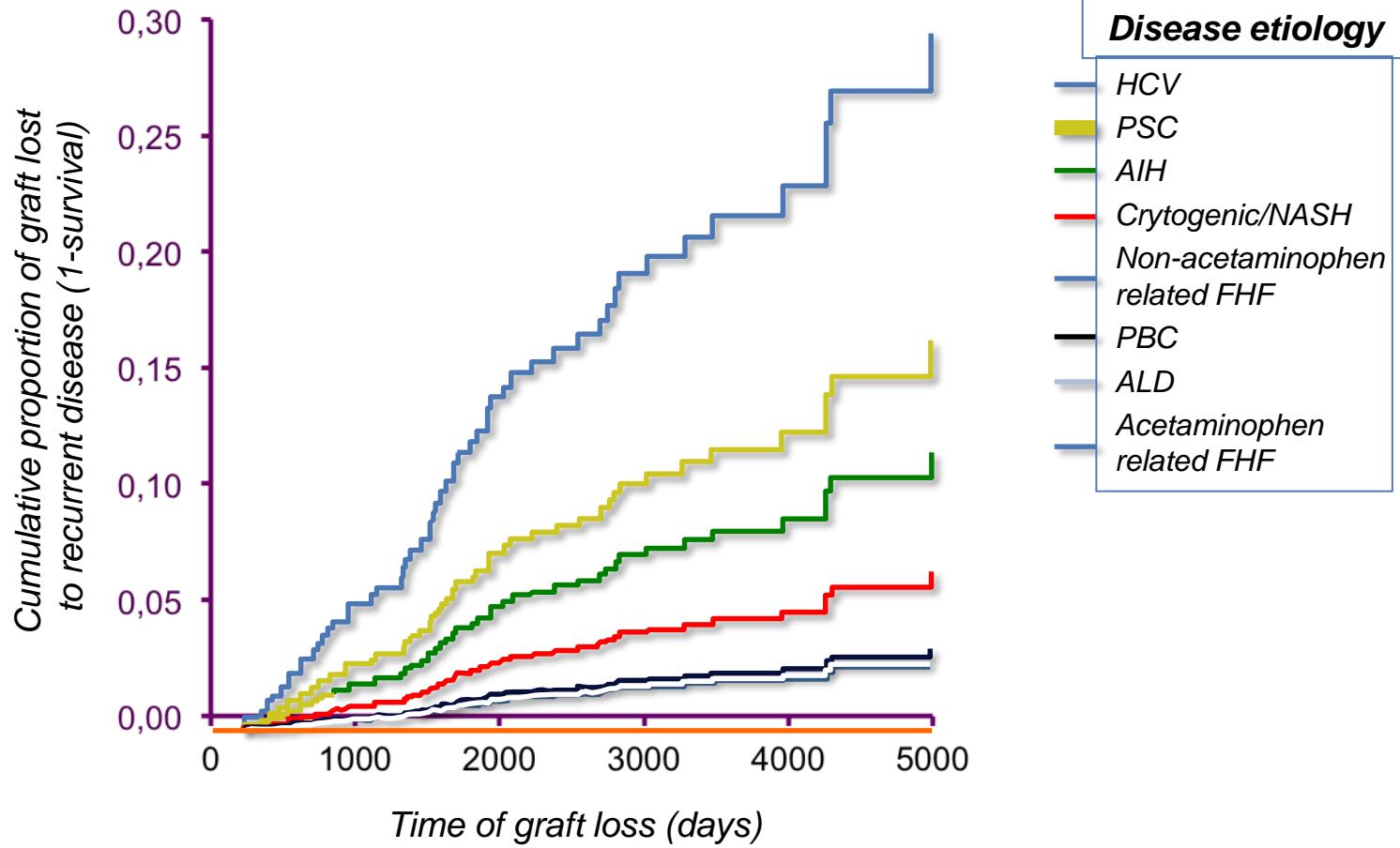
- Combinatie HBIG + NA
- rHBV RR 0.28
- Mort RR 0.44



HCV recurrence

- DAA tijdperk > 95% SVR
- Discussie : voor of na LTx?
- “MELD purgatory”
- Indien MELD > 25 wacht tot na LTx

PSC is 2^e oorzaak transplantaat verlies



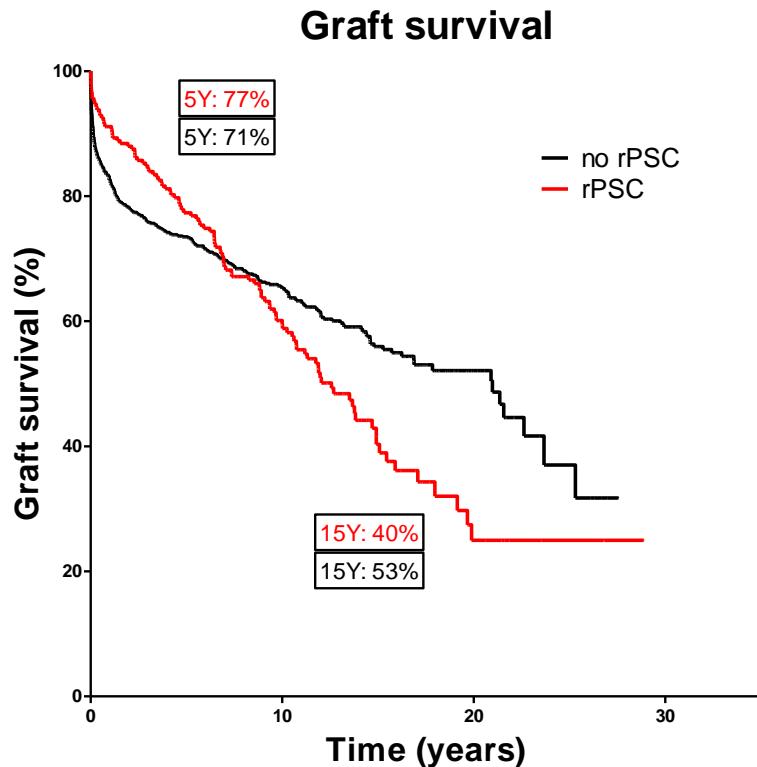
AIH, autoimmune hepatitis; ALD, alcoholic liver disease; FHF, fulminant hepatic failure; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis;

PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

Neuberger J. Liver Transplantation 2009; 15:S1–S5.

Recurrence PSC : impact op overleving

Incidentie rPSC 17.5%



Graft
Patient

HR 4.01 ($p < 0.001$)
HR 2.28 ($p < 0.001$)

	Non rPSC group (n=1059)	rPSC group (n=225)	p
2nd transplant	149 (14%)	78 (35%)	<0.001
3rd transplant	13 (1%)	16 (7%)	<0.001
4th transplant	2 (0.2%)	6 (3%)	<0.001

Osteoporose en wervelinzakking

Meeste botverlies 1^e 3-6 m

Fractuur inc 1^e jaar 20-30%

30-43% in cholestaticische leverziekten



Preventie wervelinzakking fractuur

- Optimalisatie botstatus voor transplantatie
- Laagst mogelijke dosering prednison en tacrolimus
- Suppletie van calcium en vitamine D
- I.v. 4 mg zoledroninezuur kort na transplantatie

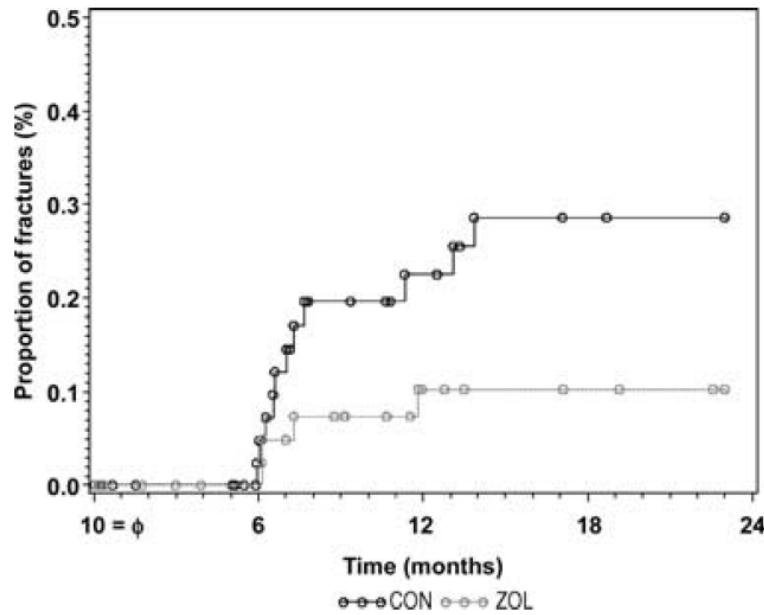


Figure 2: Primary study endpoint: fracture (log-rank test, $p = 0.050$).

Take home messages

Levertransplantatie heeft een uitstekende overleving

Galwegschade meest beduchte complicatie

Uitdagingen voor lange termijn overleving

- Metabole effecten immuunsuppressie
- Terugkeer van primaire leverziekte
- Maligniteit



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