Complicaties na levertransplantatie

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MDL arts

Dutch Liver Week 2017

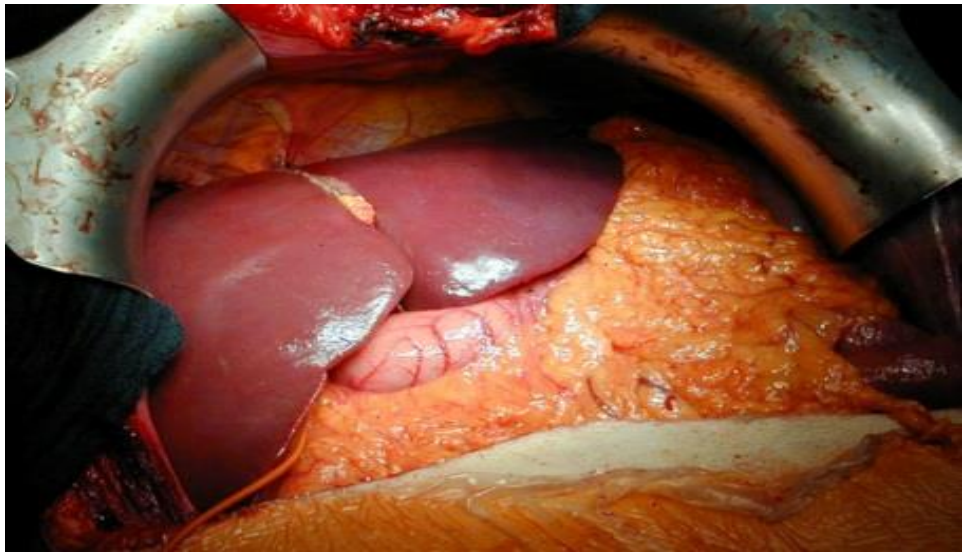
Uitkomsten na levertransplantatie

Donor populatie

Complicaties, transplantatie gerelateerd

Complicaties, immuunsuppressie gerelateerd

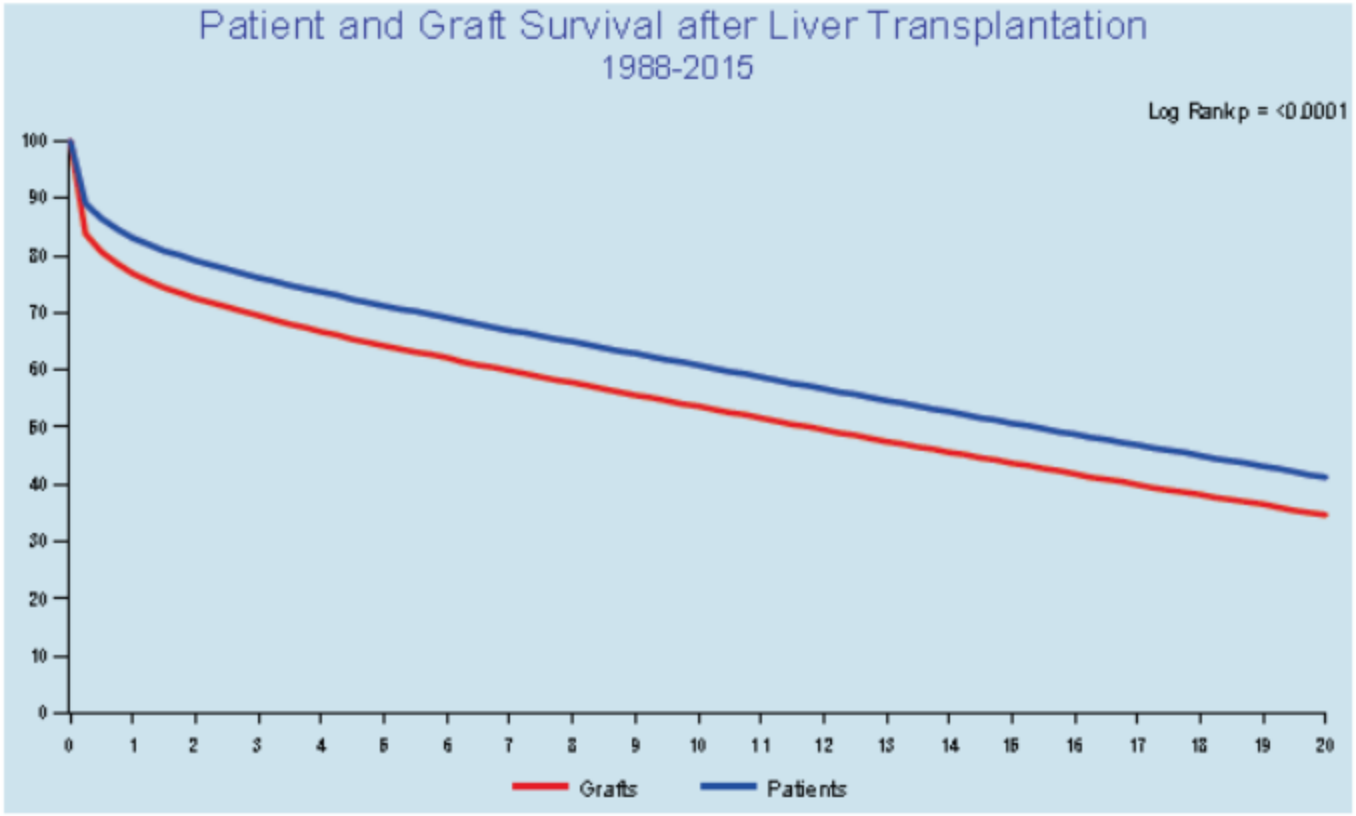
Erasmus MC



UITKOMSTEN NA LEVERTRANSPLANTATIE

Erasmus MC

Patient and Graft Survival after Liver Transplantation
1988-2015

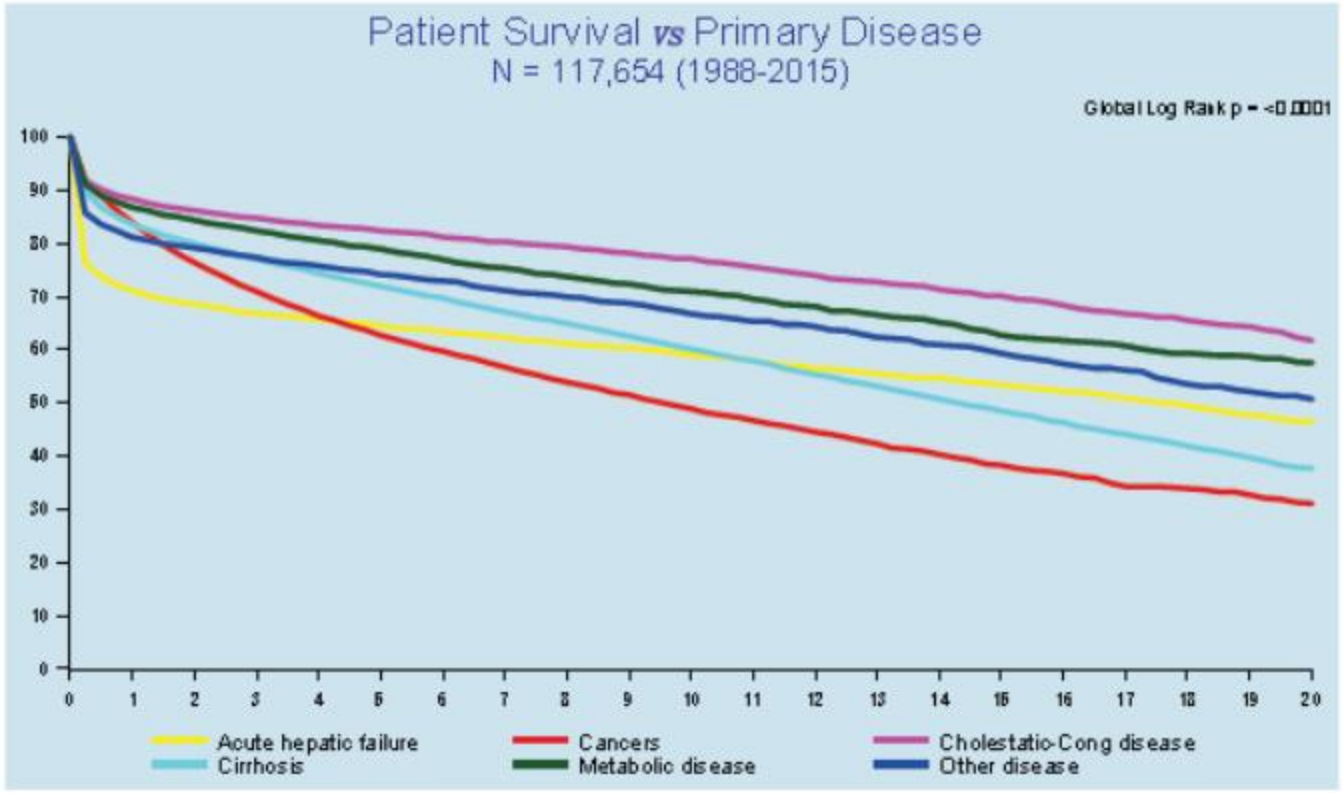


Survival %

population	1 yr	3 yrs	5 yrs	8 yrs	10 yrs	12 yrs	14 yrs	16 yrs	18 yrs	20 yrs
Grafts	77%	69%	64%	58%	54%	50%	46%	42%	38%	35%
Patients	83%	76%	71%	65%	61%	57%	53%	49%	45%	41%

Number of exposed patients

	Total	1 yr	3 yrs	5 yrs	8 yrs	10 yrs	12 yrs	14 yrs	16 yrs	18 yrs	20 yrs
Grafts	133411	87999	64963	50360	33130	24684	17760	12382	8221	5061	2961
Patients	120116	85570	64024	50091	33385	25140	18274	12885	8676	5439	3245



Details : Log rank p

		probs
Acute	Ca	0.65
Acute	Chol_	<0.0001
Acute	Cirrh	<0.0001
Acute	Mtab	<0.0001
Acute	Oth	<0.0001
Ca	Chol_	<0.0001
Ca	Cirrh	<0.0001
Ca	Mtab	<0.0001
Ca	Oth	<0.0001
Chol_	Cirrh	<0.0001
Chol_	Mtab	<0.0001
Chol_	Oth	<0.0001
Cirrh	Mtab	<0.0001
Cirrh	Oth	<0.0001
Mtab	Oth	<0.0001

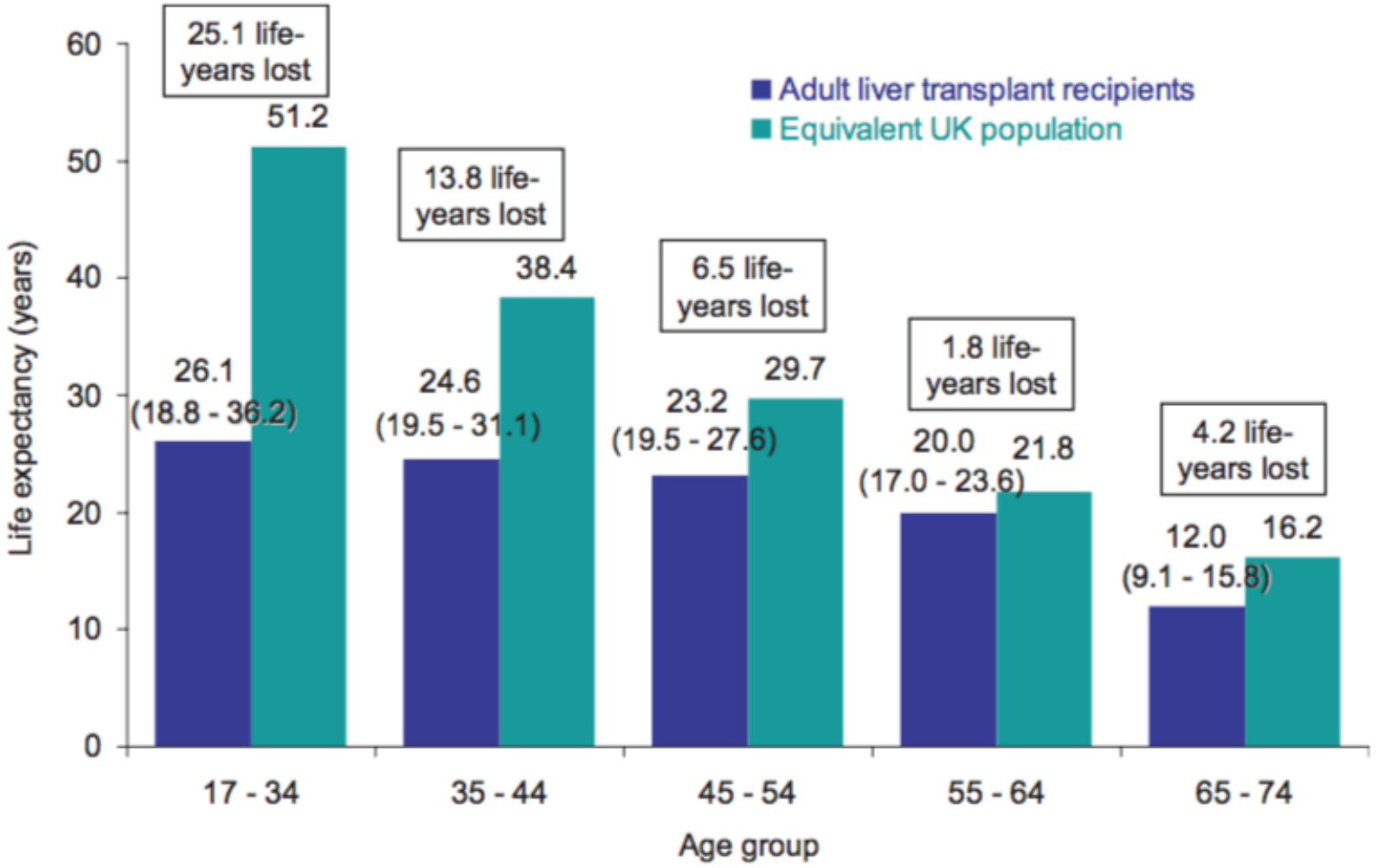
Survival %

Main_disease	1 yr	3 yrs	5 yrs	8 yrs	10 yrs	12 yrs	14 yrs	16 yrs	18 yrs	20 yrs
Acute hepatic failure	71%	67%	64%	61%	59%	57%	55%	52%	49%	46%
Cancers	84%	71%	63%	54%	49%	44%	40%	37%	34%	31%
Cholestatic-Cong disease	88%	85%	82%	79%	77%	74%	71%	68%	66%	62%
Cirrhosis	84%	77%	72%	65%	60%	55%	51%	46%	42%	38%
Metabolic disease	87%	82%	79%	74%	71%	68%	65%	62%	59%	57%
Other disease	81%	77%	74%	70%	67%	64%	61%	57%	53%	51%

Number of exposed patients

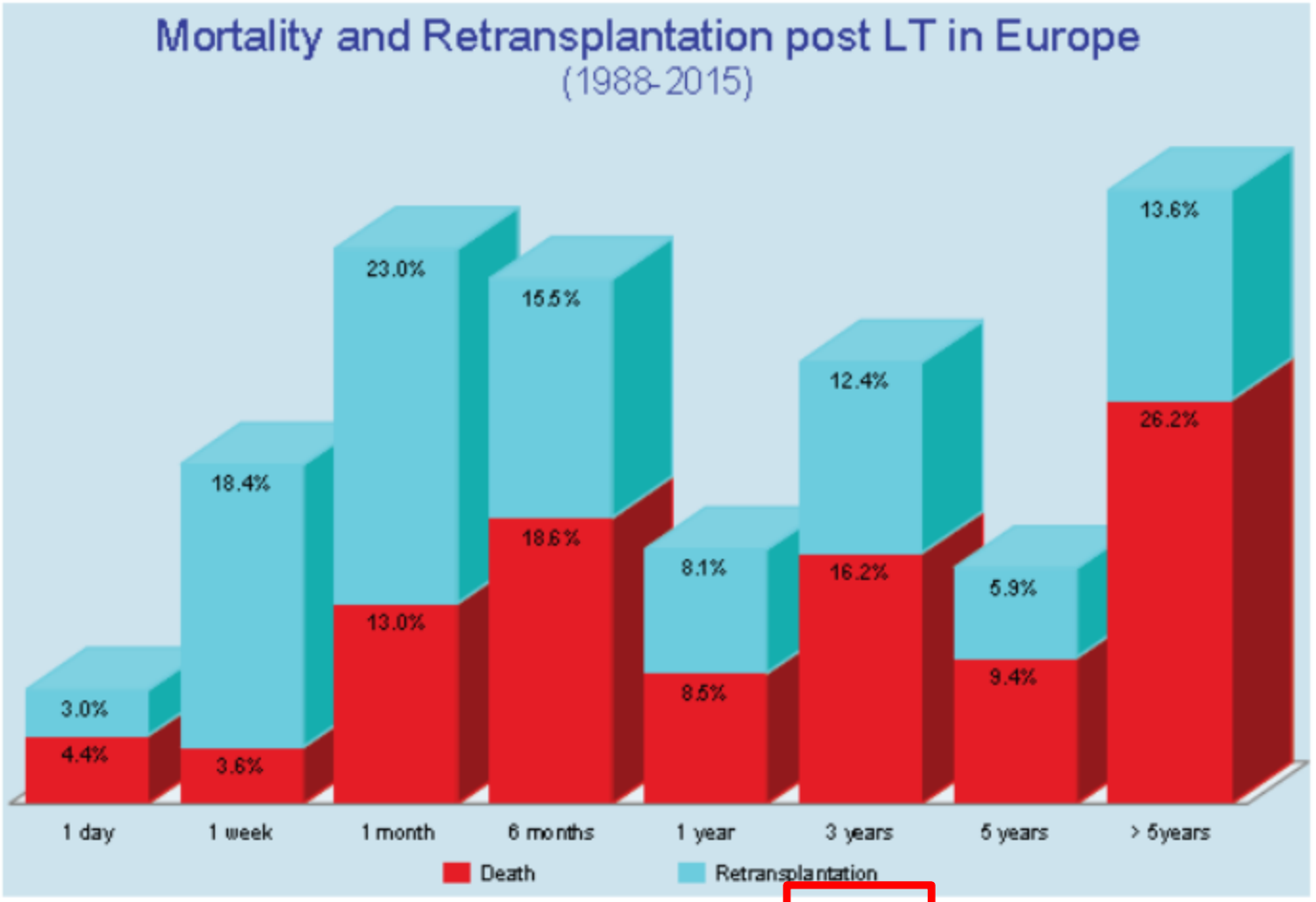
	Total	1 yr	3 yrs	5 yrs	8 yrs	10 yrs	12 yrs	14 yrs	16 yrs	18 yrs	20 yrs
Acute hepatic failure	8836	5390	4177	3420	2410	1872	1434	1076	768	512	323
Cancers	19623	13910	8946	6150	3266	2137	1375	853	523	286	166
Cholestatio-Cong disease	11568	8601	6693	5388	3829	3055	2299	1649	1168	725	427
Cirrhosis	66051	48282	36983	29347	19852	14905	10775	7514	4886	2972	1700
Metabolic disease	6636	4843	3721	2939	1893	1481	1096	789	555	360	235
Other disease	4940	3427	2683	2172	1605	1236	924	688	504	365	222

Overleving na LTx vs. algemene bevolking



Barber Gut 2007

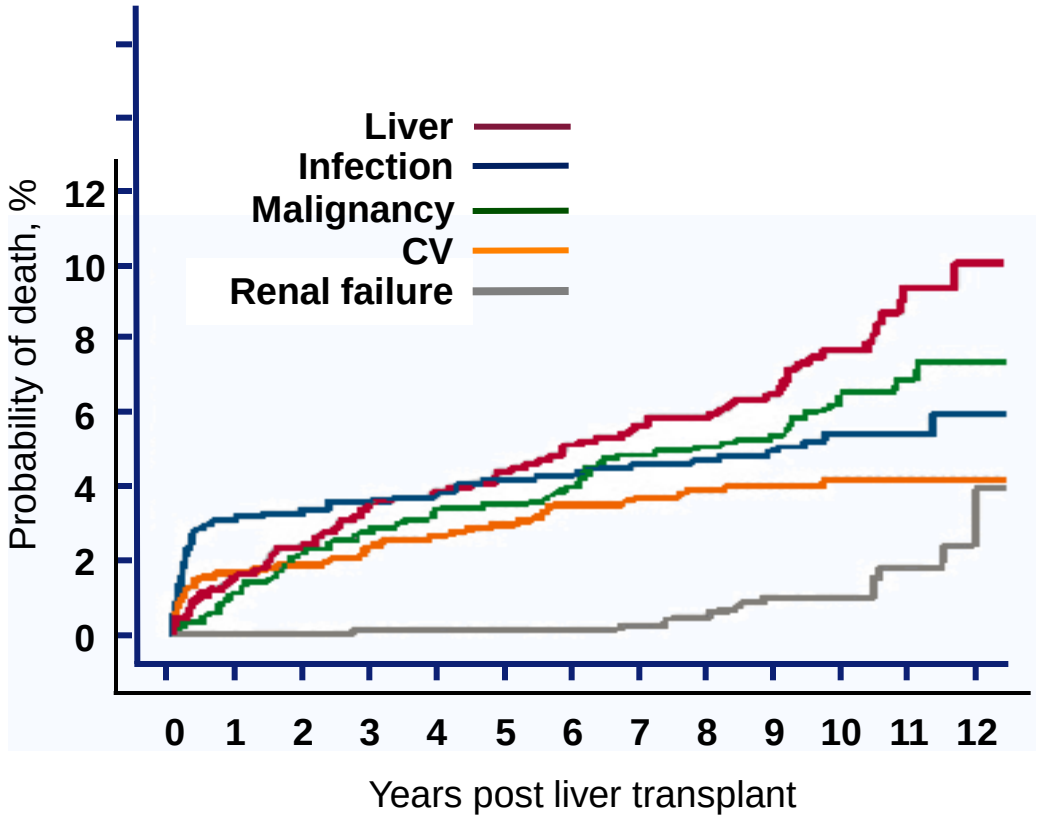
Mortality and Retransplantation post LT in Europe
(1988-2015)



Cumulative proportions	1 day	1 week	1 month	6 months	1 year	3 years	5 years	>5 years
Death	4%	8%	21%	40%	48%	64%	74%	100%
Retransplantation	3%	21%	44%	60%	68%	81%	86%	100%

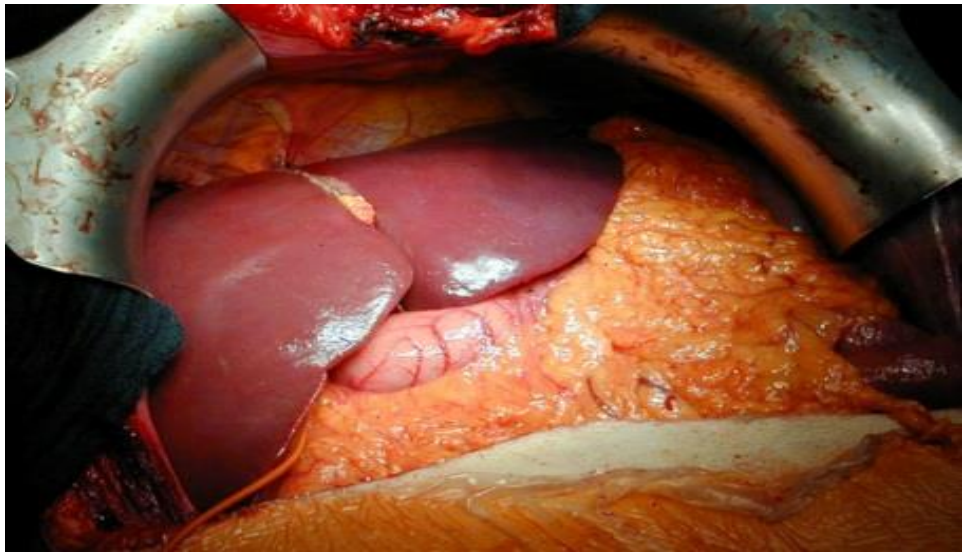
Oorzaken van overlijden op lange termijn

NIDDK Database: 10-year median follow-up



Watt et al. *Am J Transplant* 2010

Erasmus MC



DONOR POPULATIE
ANNO NU

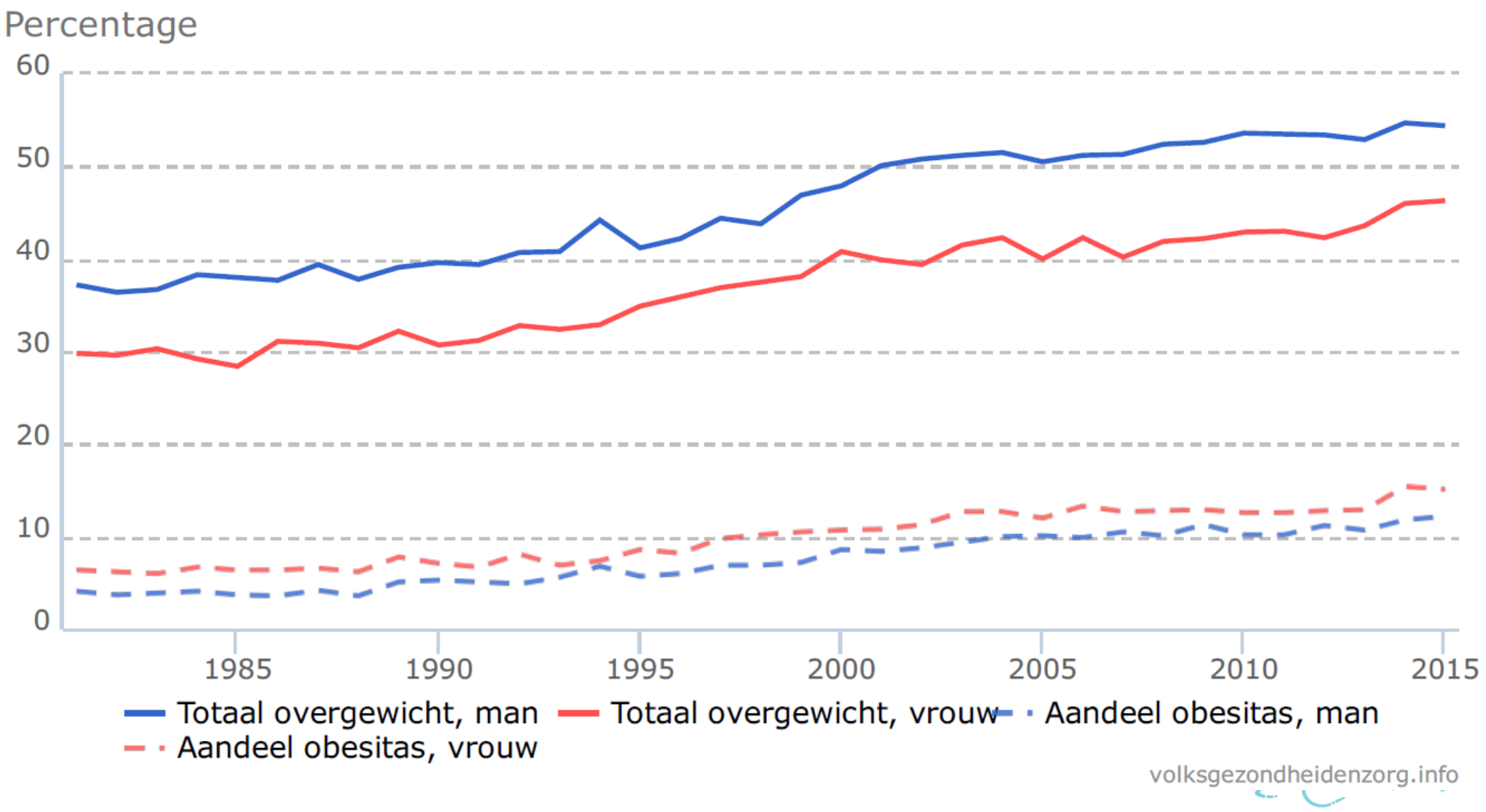
Erasmus MC

De ideale donor …

De realiteit …

Percentage volwassenen met overgewicht en obesitas van 1981-2015

20 jaar en ouder



Toename donor leeftijd

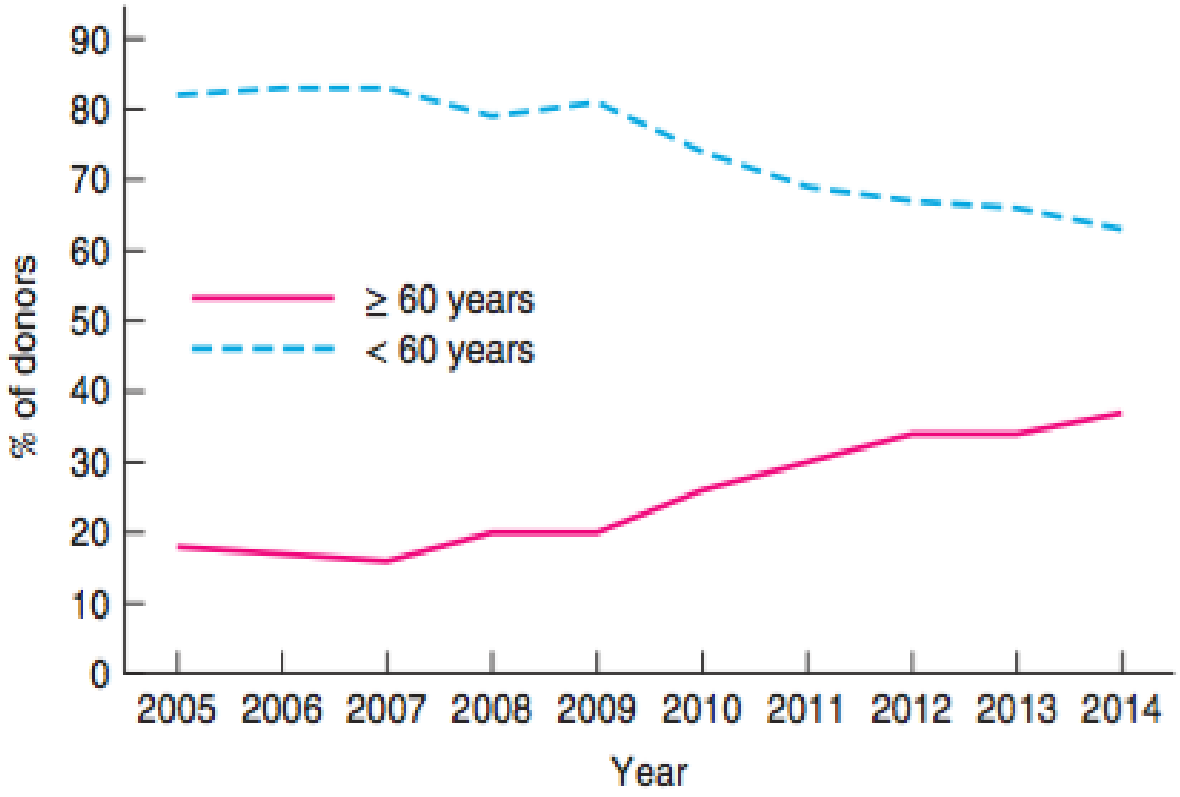


Fig. 1 Percentage of deceased donors aged at least 60 years in the UK (National Health Service Blood and Transplant[8])

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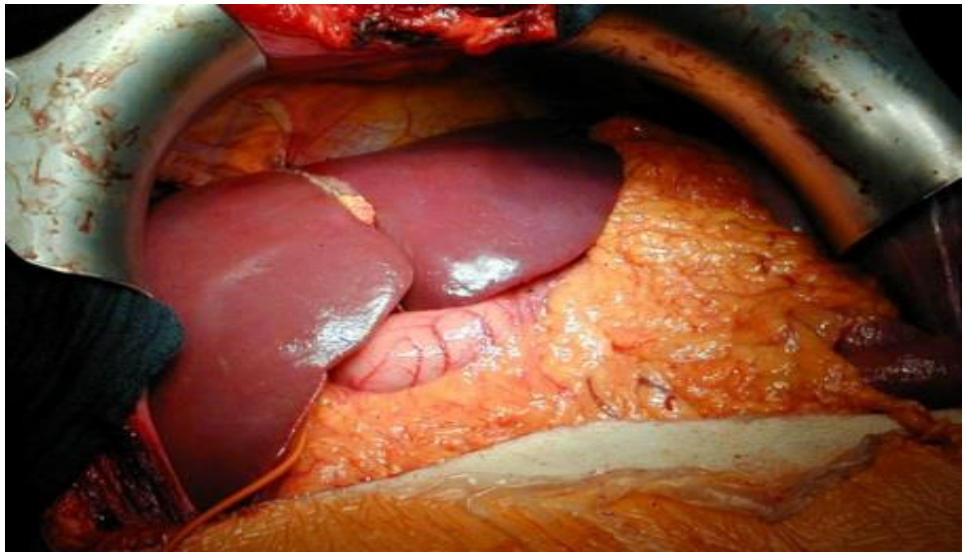

COMPLICATIES

TRANSPLANTATIE GERELATEERD

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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 ≥ 170 µmol/l op dag 7

INR ≥ 1.6 op dag 7

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

Incidentie: 23%

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

Olthoff et al. Liver Transplantation 2010

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

Duffy et al J Am Coll Surg 2009

Galwegcomplicaties

Combinatie techniek + ischemie

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

<u>Behandeling</u>

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

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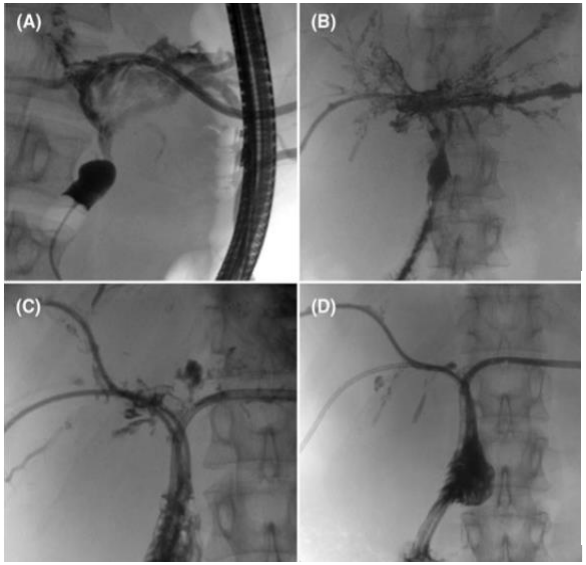
Karimian et al. Curr Opin Organ Transplant 2014

Gallekkage

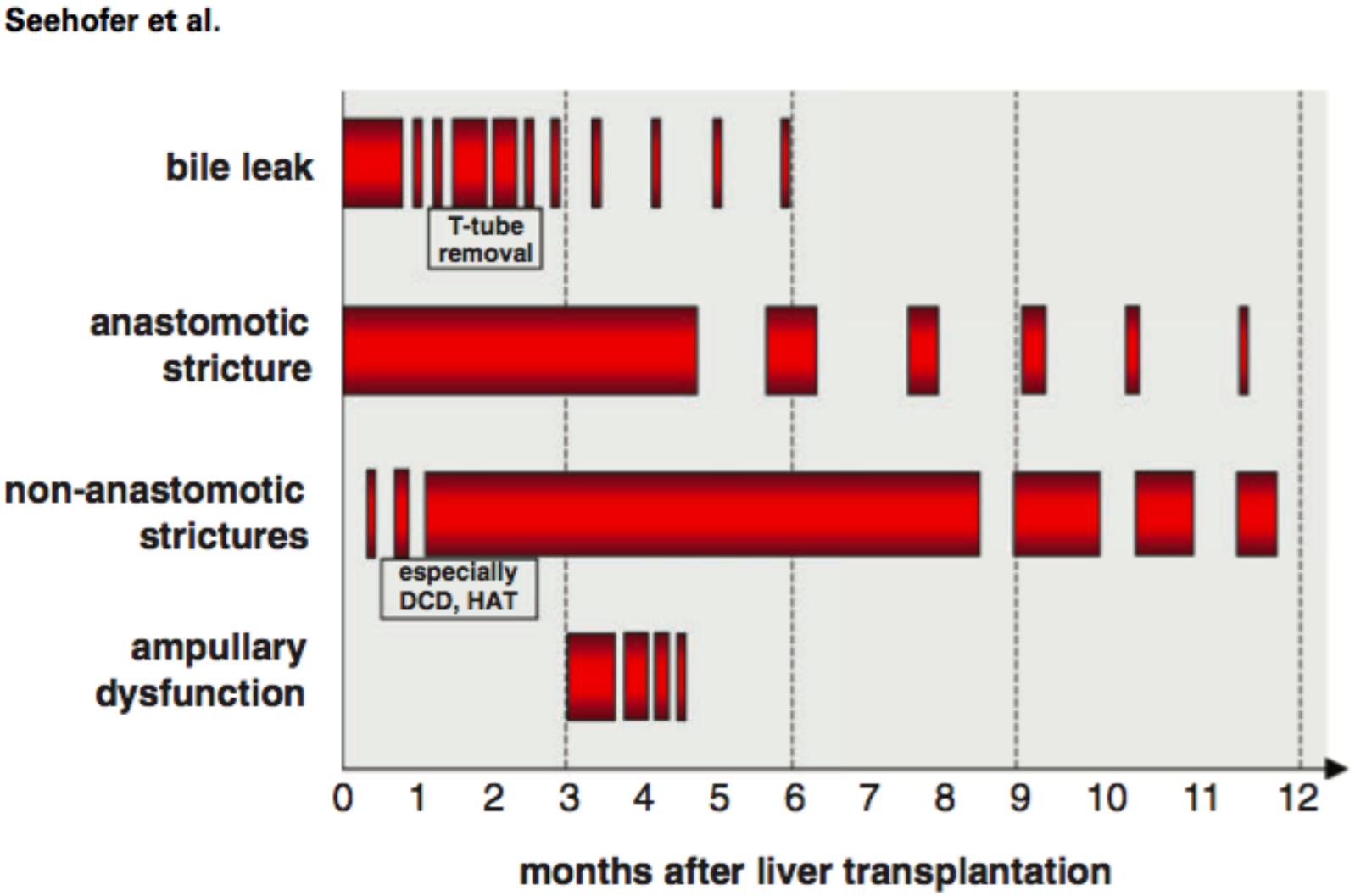
Stenose anastomose

Stenose HJ

Ischaemic type biliary lesions (ITBL)



Galwegcomplicaties in de tijd



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

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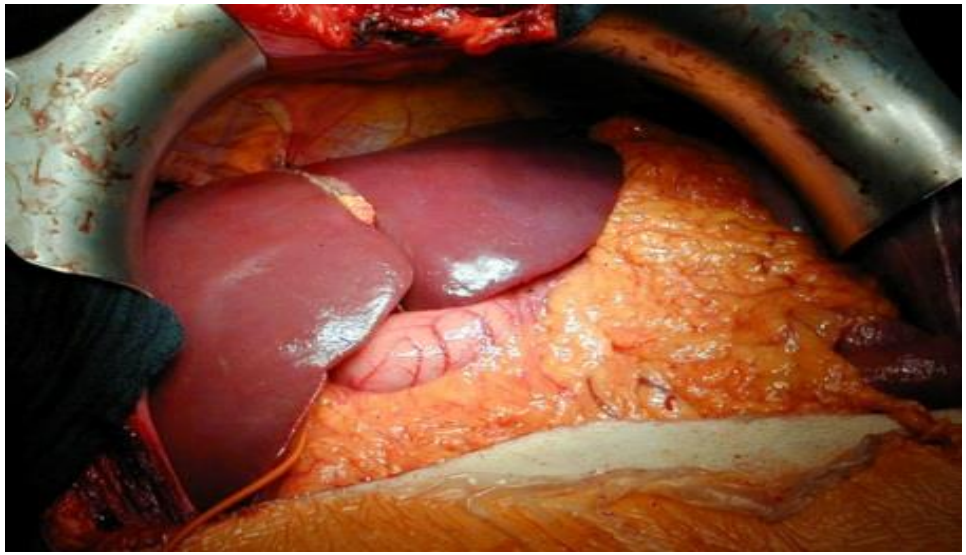
Dubbeld J, Br J Surg, 2010



COMPLICATIES

IMMUUNSUPPRESSIE GERELATEERD

Erasmus MC

Rejectie

rasmus MC

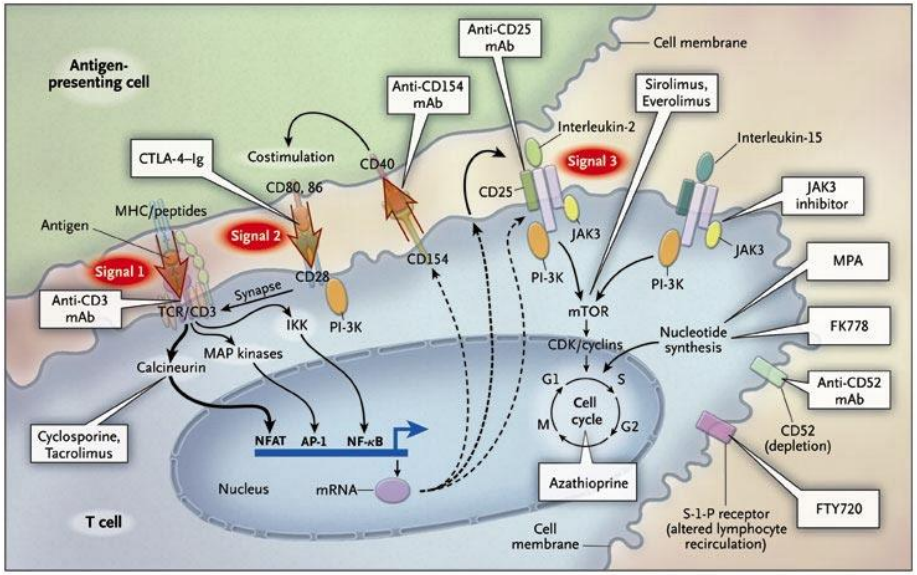
Standaard immunosuppressie

Inductie
- 500 mg methylprednisolon anhepatische fase
- 20 mg Basiliximab dag 0 en 4

Start
- CellCept 2 dd 1000 mg
- Prednison 20 mg
- Tacrolimus vanaf dag 5

Onderhoud
- Tacrolimus monotherapie
- Prednison 10 mg, taper in 6m

Aanpassing
- tijd na LTx
- bijwerkingen
- rejectie



Trunecka et al. DIAMOND study Am J Transpl 2015

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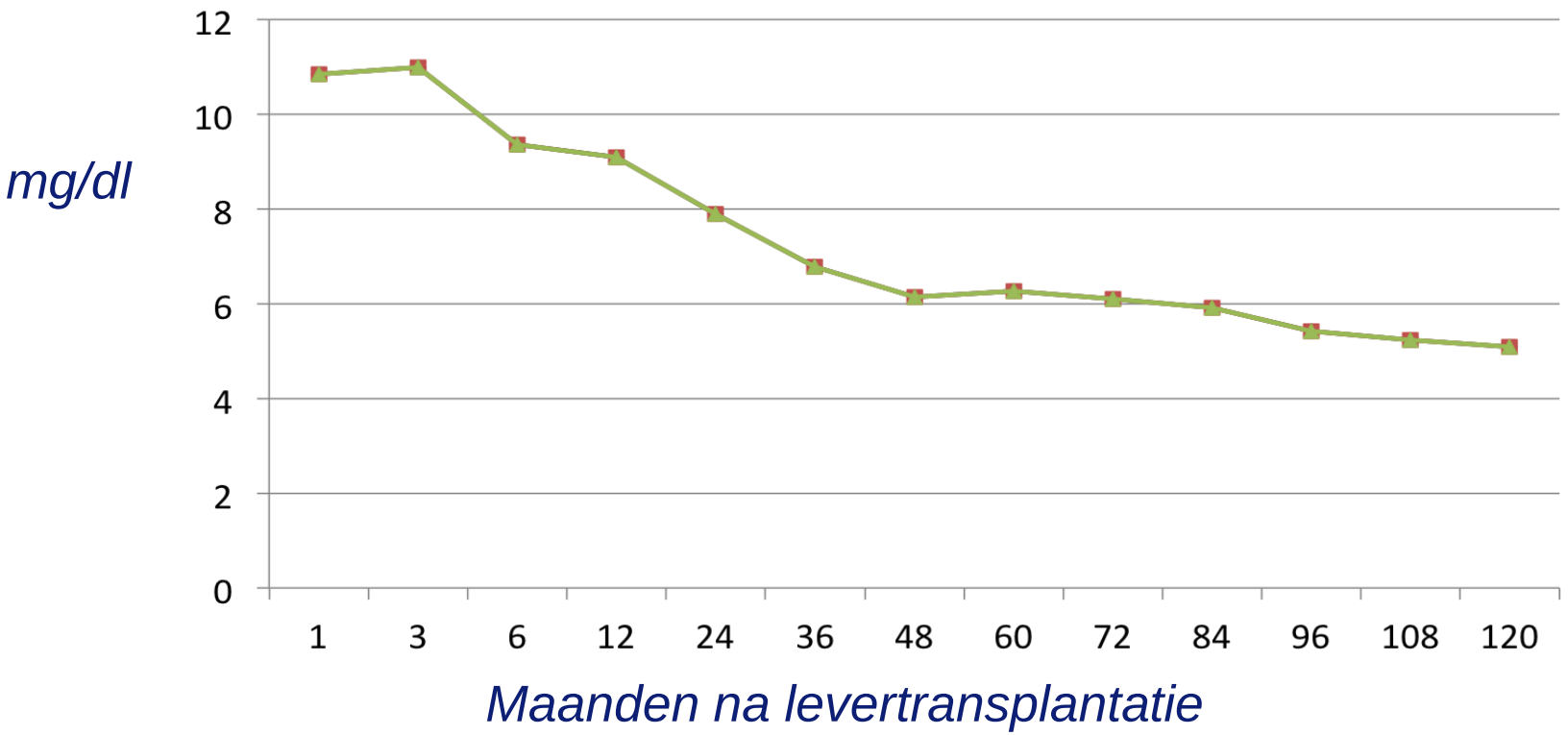
Tacrolimus dalspiegel in tijd



TARGET

week 0-6	6-10 mg/dl
week >6	4-8 mg/dl

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

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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

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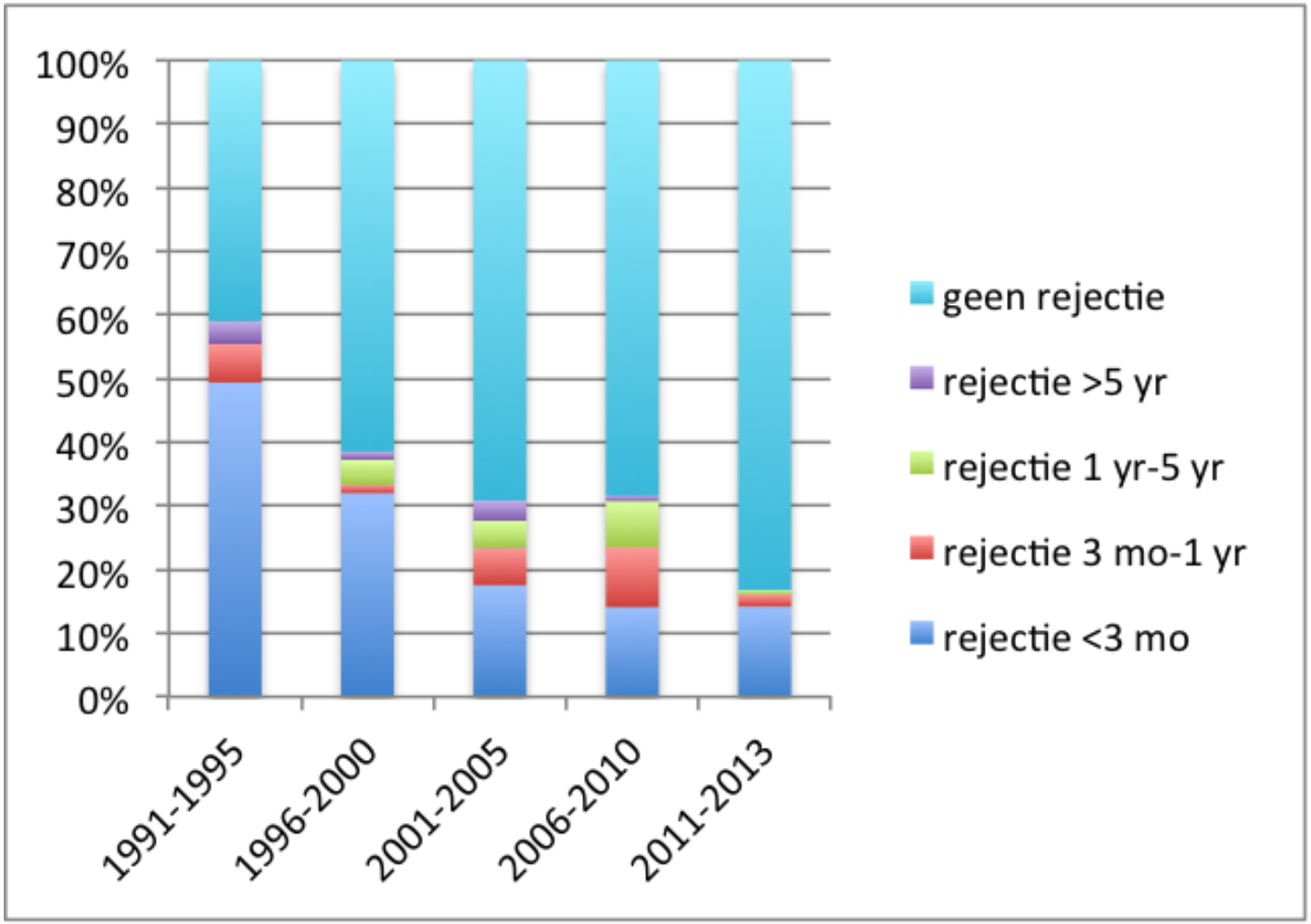
Afname aantal behandelde acute afstotingen



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Infectie

Erasmus MC

?

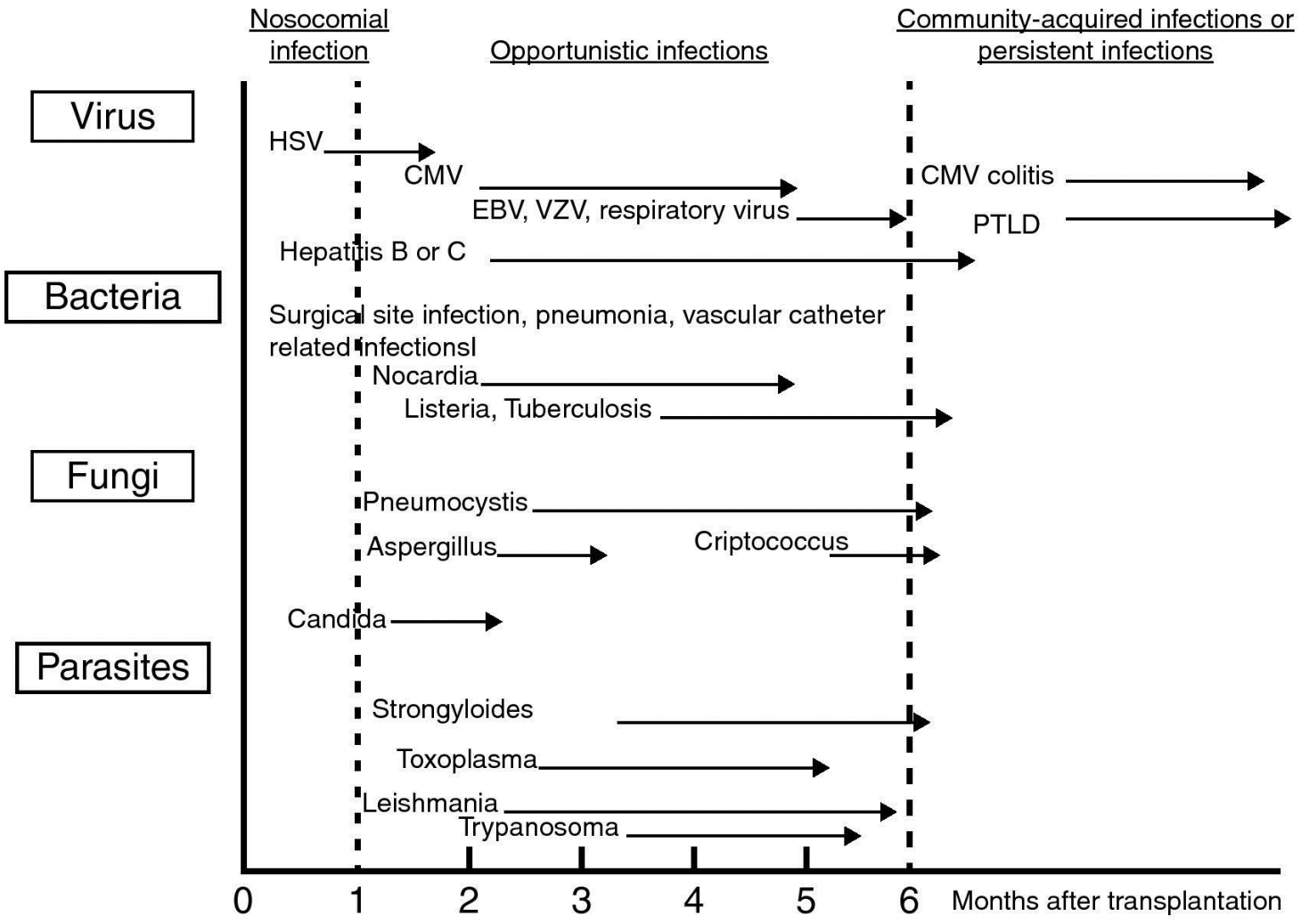
In de eerste maand na levertransplantatie is de patiënt het meest ‘at risk’ voor opportunistische infecties

1. Waar

2. Niet waar

Erasmus MC

Infecties na orgaantransplantatie



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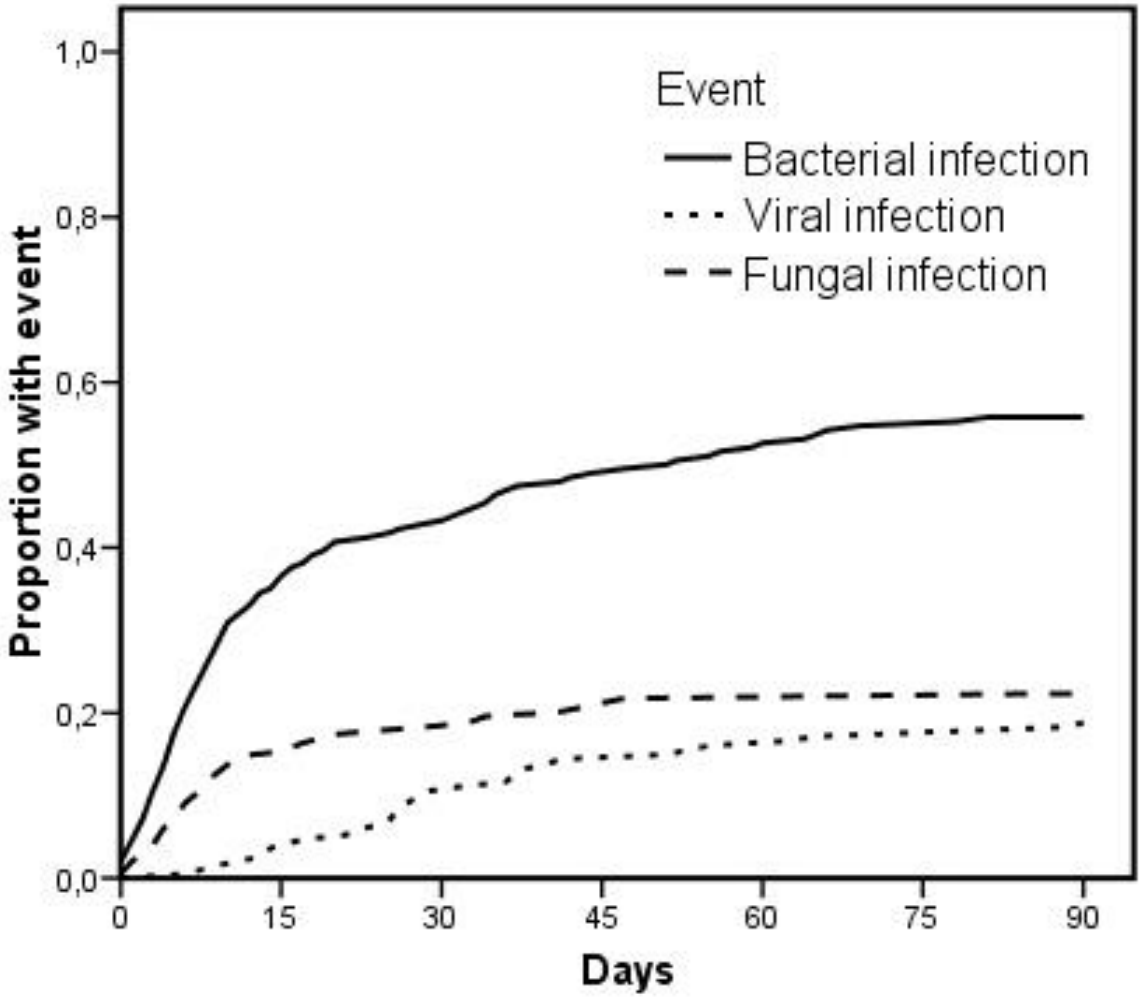
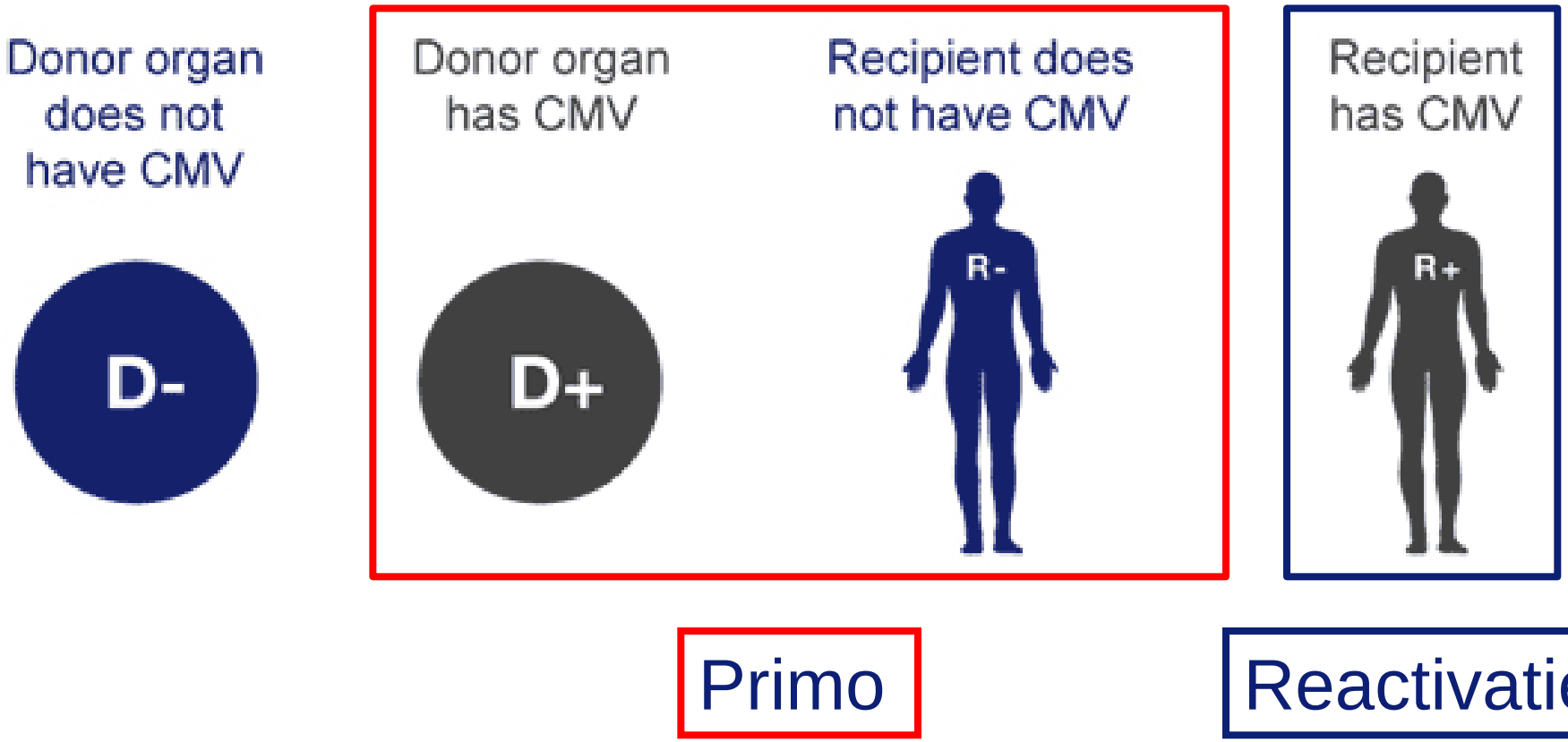
Fishman NEJM 2007

Infecties na levertransplantatie



Erasmus MC
Universitair Medisch Centrum Rotterdam

CMV infectie



Valgancylovir

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

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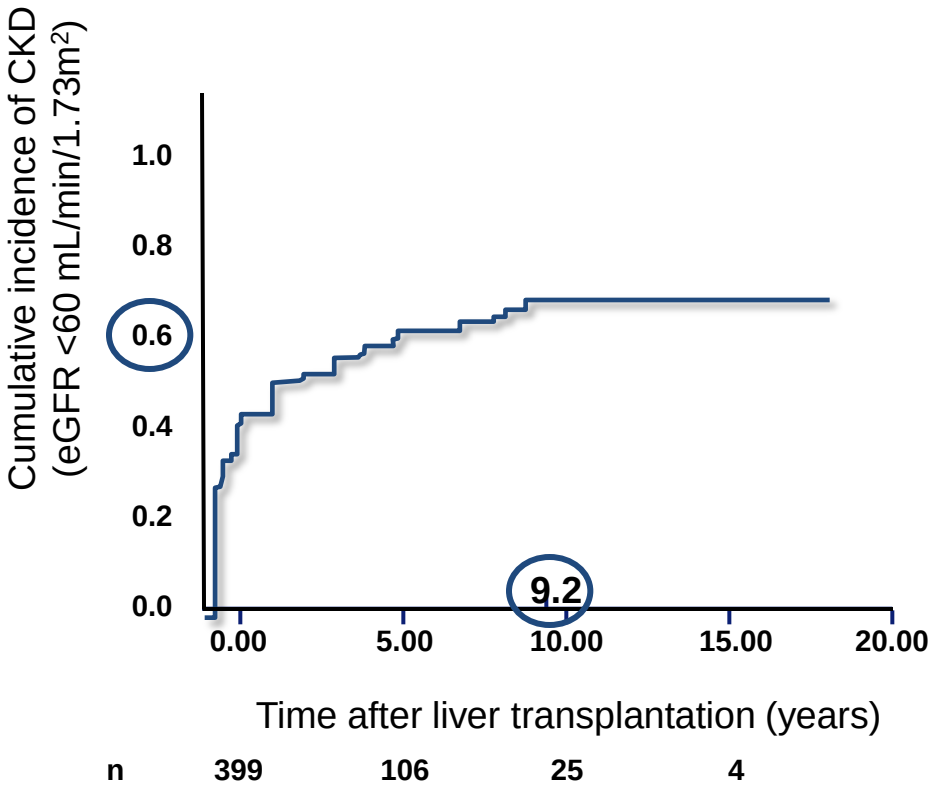
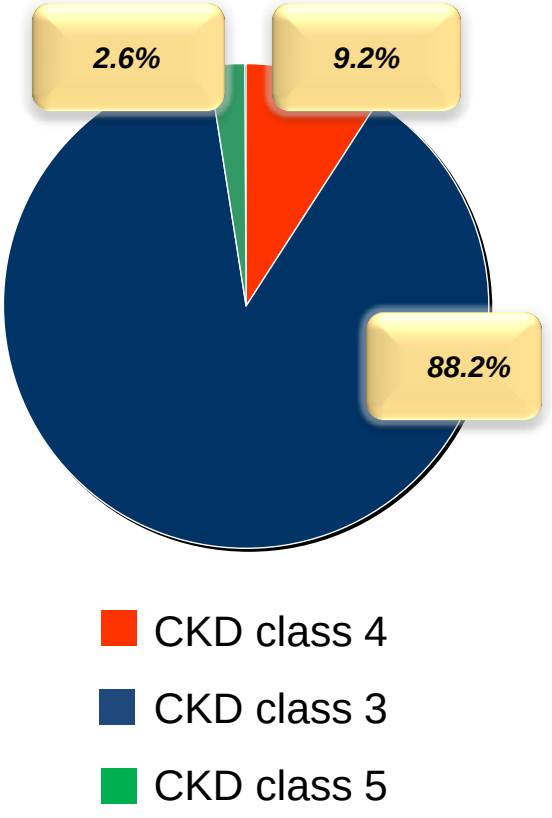
Chronische nier insufficientie

Erasmus MC

Chronische nierziekte na LTx

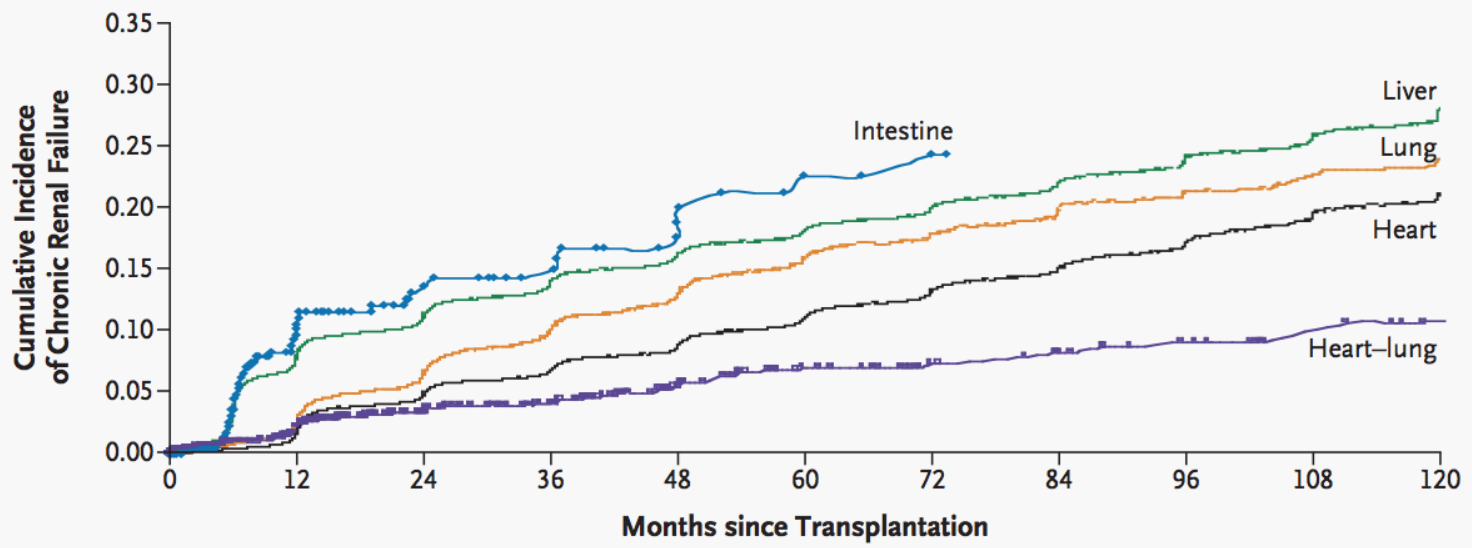




Tapirdirmaz O et al, 2014.

Erasmus MC

Nierfalen meest frequent na LTx



No. at Risk											
Heart–lung	576	375	295	219	194	156	133	107	72	46	30
Heart	24,024	19,885	17,238	14,687	12,341	10,022	7997	6104	4526	3096	1991
Intestine	228	152	110	84	57	33	23	13	8	5	5
Liver	36,849	28,495	24,041	19,508	15,724	12,564	9844	7345	5292	3614	2261
Lung	7,643	5,633	4,316	3,184	2,327	1,629	1136	745	468	258	133

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.

Ojo et al. NEJM 2003

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

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Schlitt 2001; Pageaux 2006; Cicinnati 2007; Bisselli 2012; de Simone 2012; Massetti 2010; Fischer 2012

Metabole effecten immuunsuppressie

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De meest voorkomende metabole complicatie na LTx is

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

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Bijwerkingen immuunsuppressie

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

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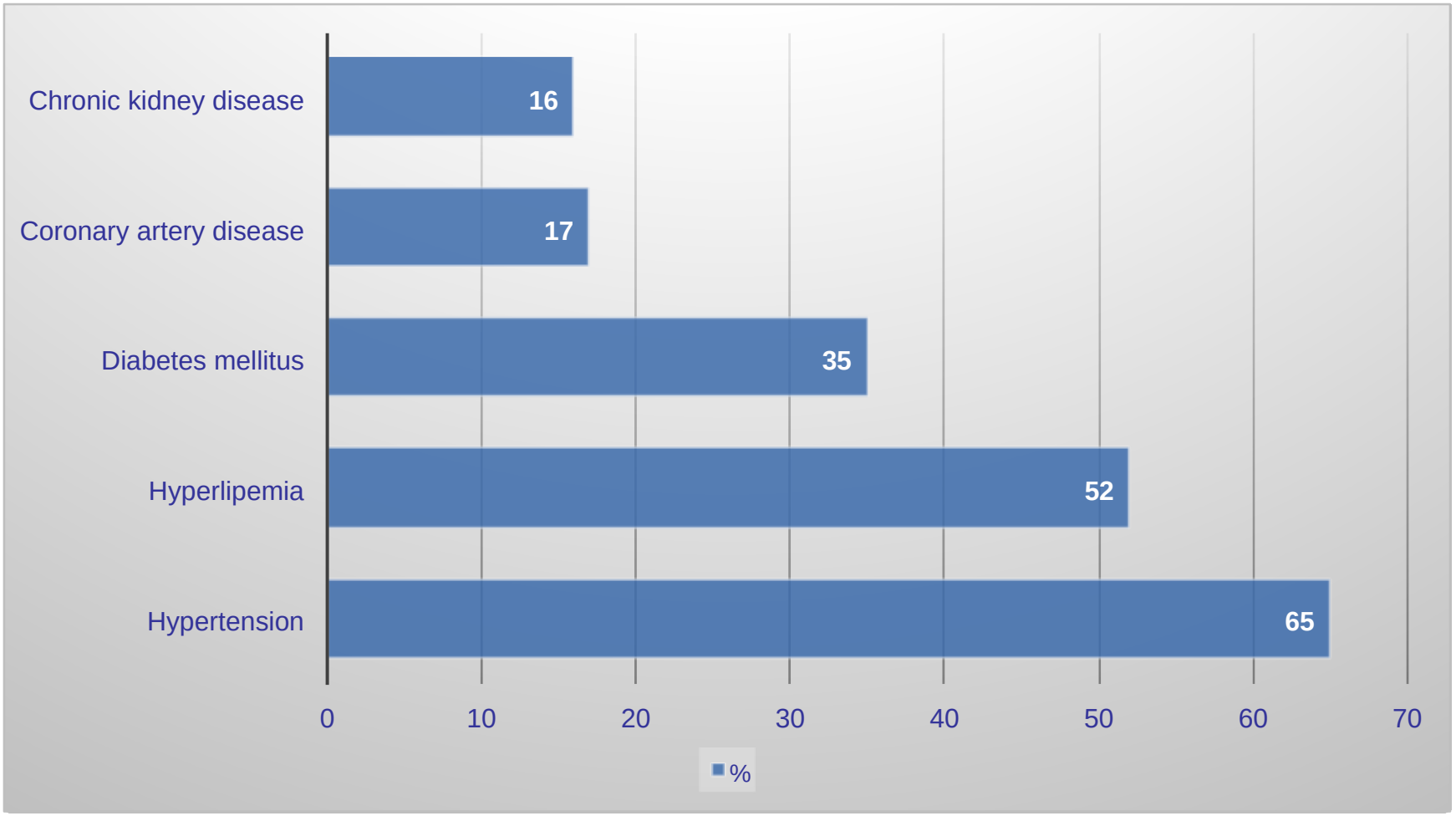
Singh and Watt. Mayo Clin Proc 2012

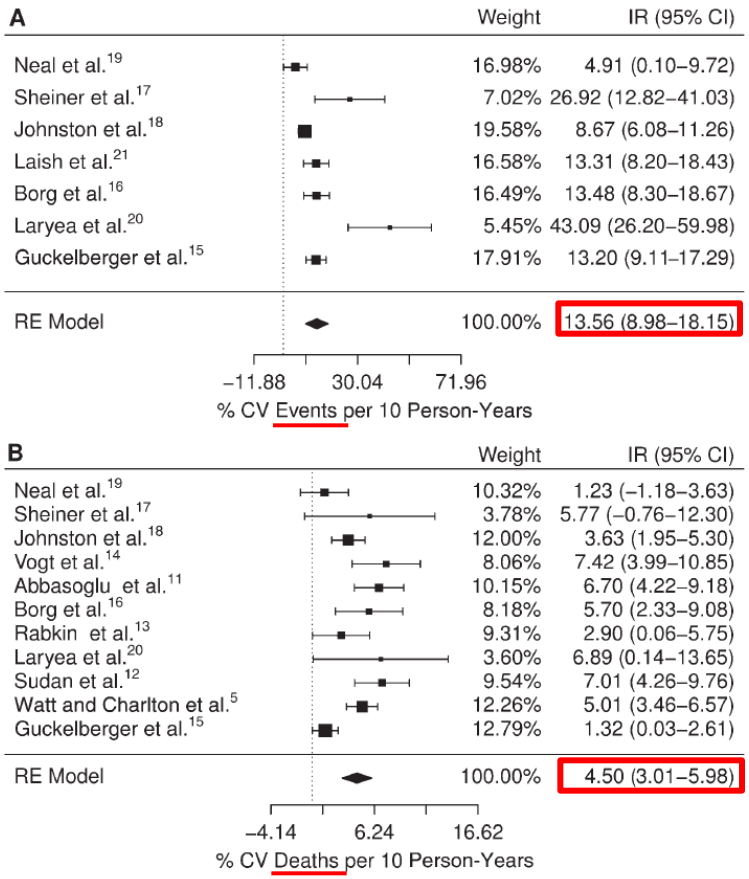
Meest voorkomende metabole complicaties



Erasmus MC

Singh and Watt. Mayo Clin Proc 2012

LTx onafhankelijke RF cardiovasculaire events



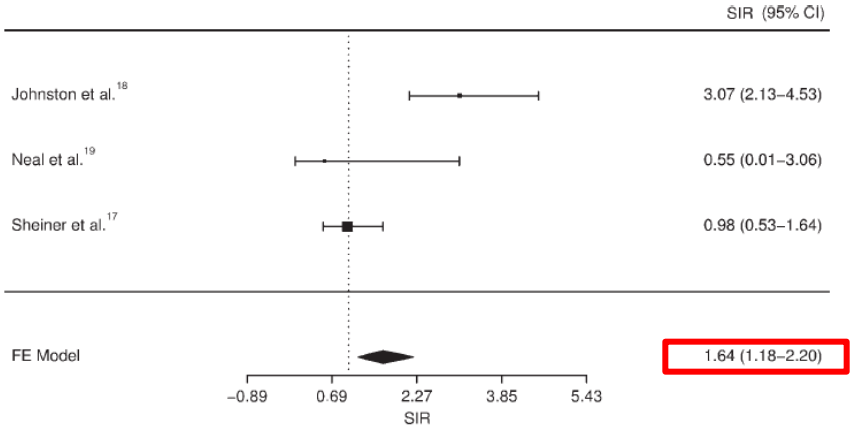
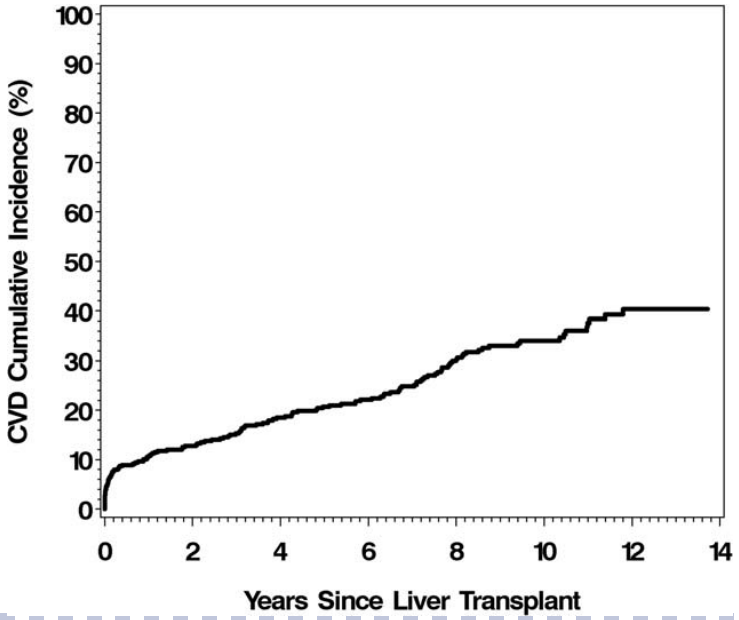


Figure 3. Pooled estimates of SIRs for liver transplant recipients versus the general population.



Madhwal et al. Liver transplant 2012; Fussner et al. Liver Transplantation 2015

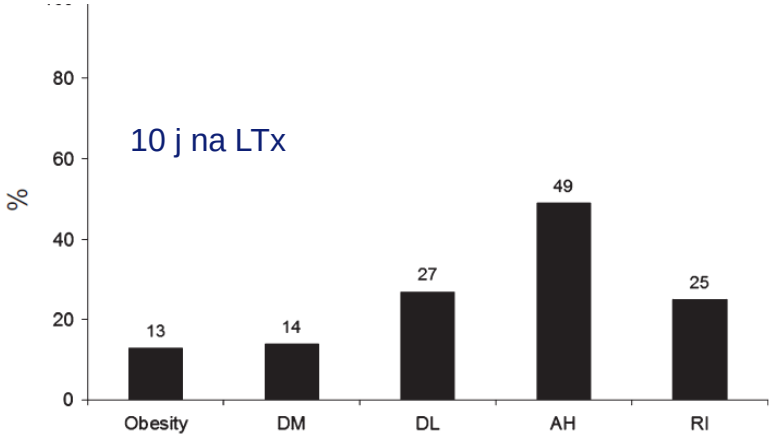
Metabool syndroom

Meeste gewichtstoename in 1e j

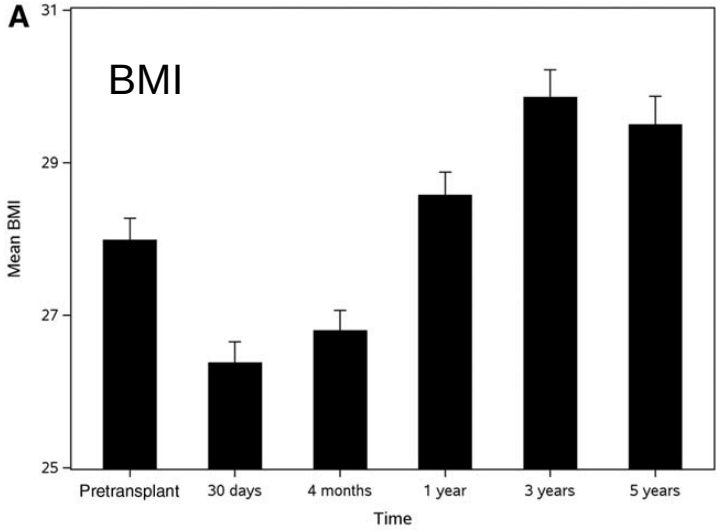
67% verhoogt calorie inname

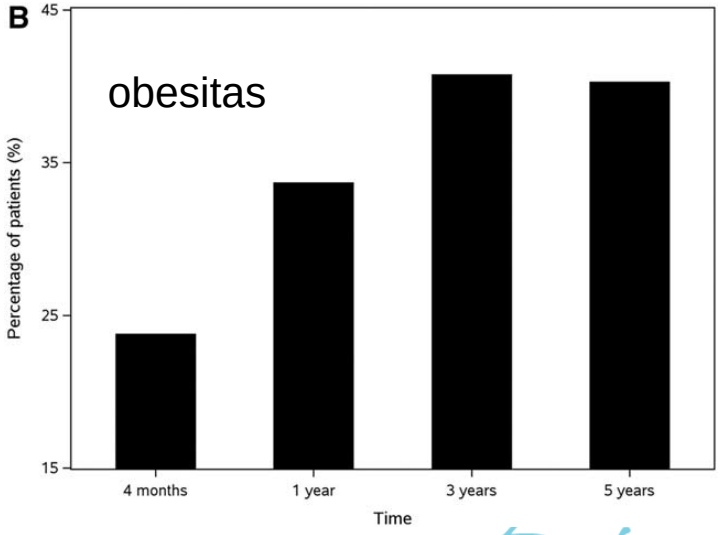
Slechts 25% fysiek actief

Risico metabool syndroom blijft toenemen



DM = Diabetes mellitus; DL = Dyslipidemia; AH = arterial hypertension; RI = renal insufficiency

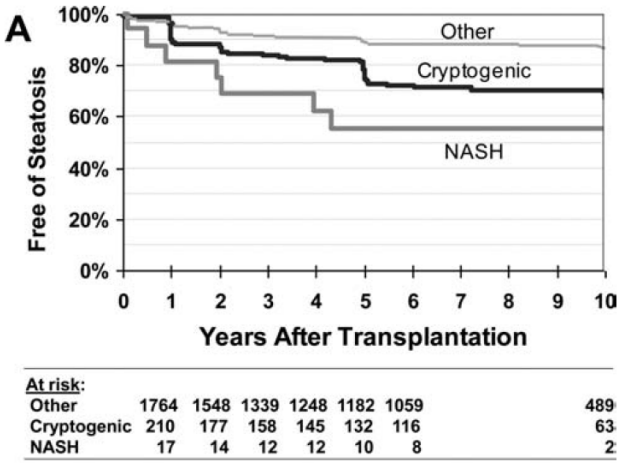




Fussner et al. Liver Transplantation 2015; Rubin et al. Transpl Int 2013

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

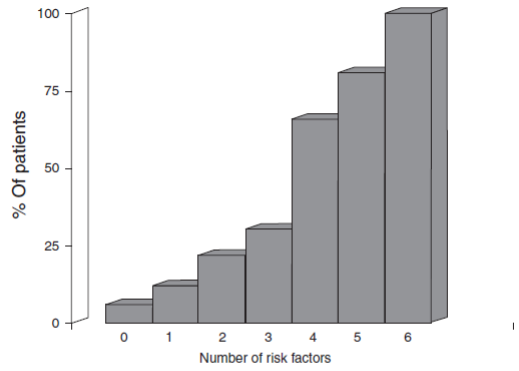
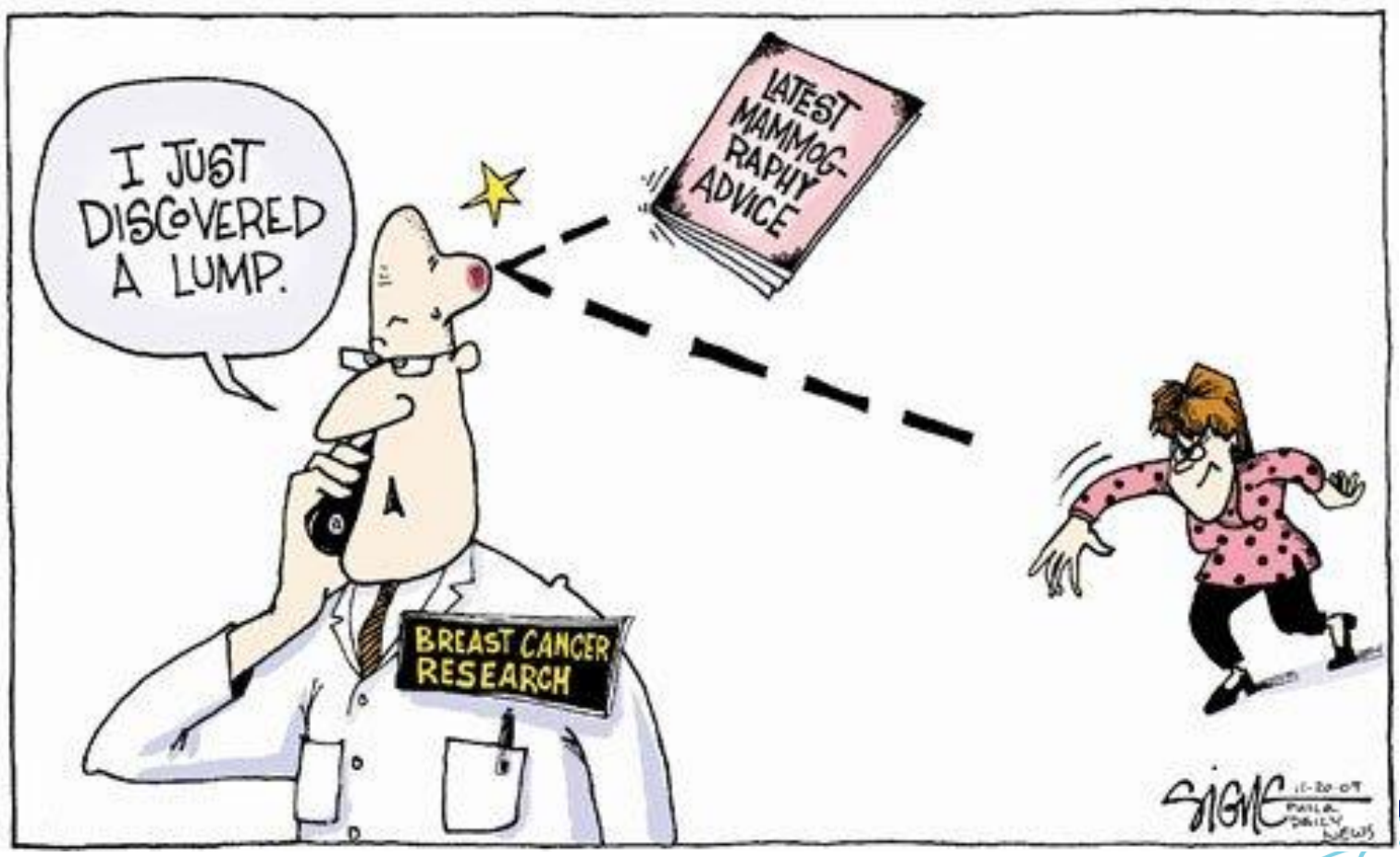


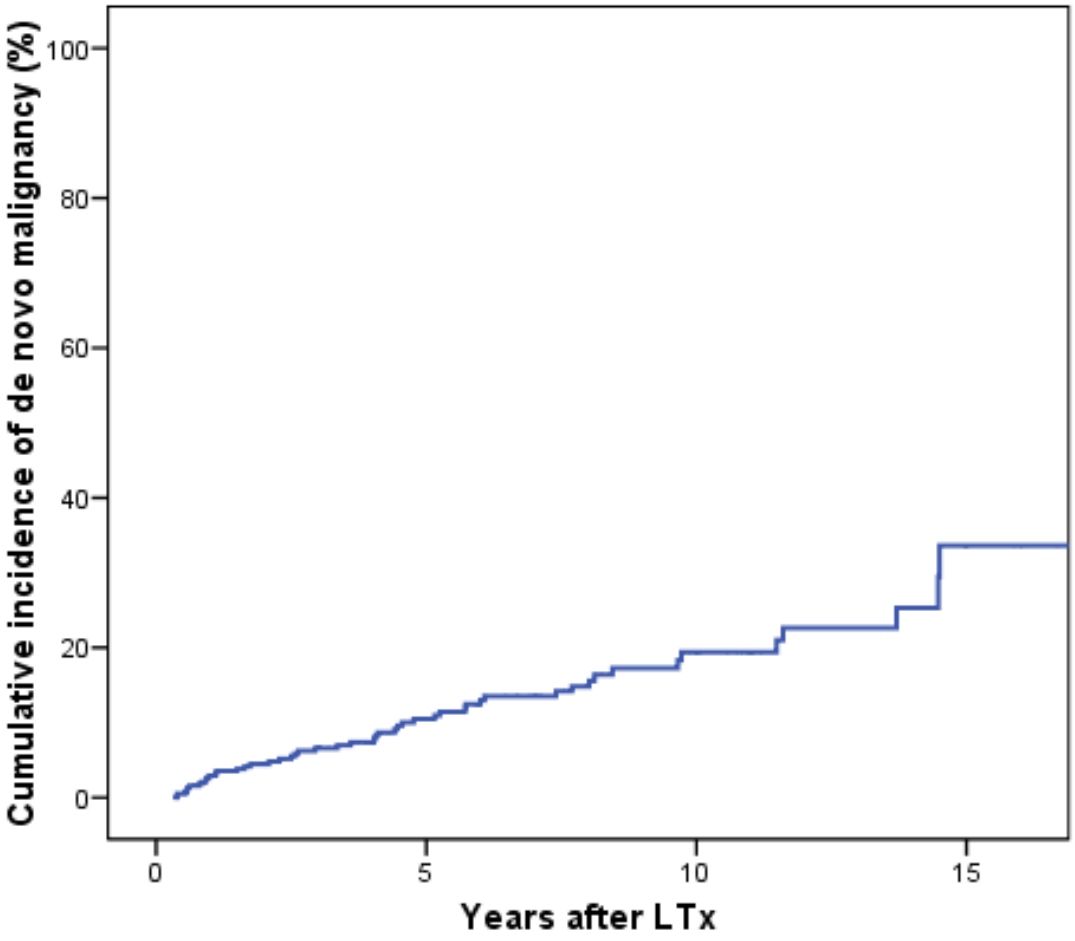
Figure 2. Relationship between the number of risk factors (obesity at the time of liver biopsy, tacrolimus-based regimen, diabetes mellitus, hyperlipidemia, arterial hypertension, alcoholic cirrhosis as primary indication for LT, and liver graft steatosis) and the risk of non-alcoholic fatty liver disease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

Yalamanchili Liver Transplantation 2010; Dumortier Am J Gastro 2010; Contos Liver Transplantation 2001; Charlton Liver Transplantation 2001; Ong Liver Transplantation 2001; Bhagat Liver Transplantation 2009; Seo Liver Transplantation 2007; Kim Clin Transplantation 2014; El Atrache Clin Transplantation 2012

Maligniteit



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)

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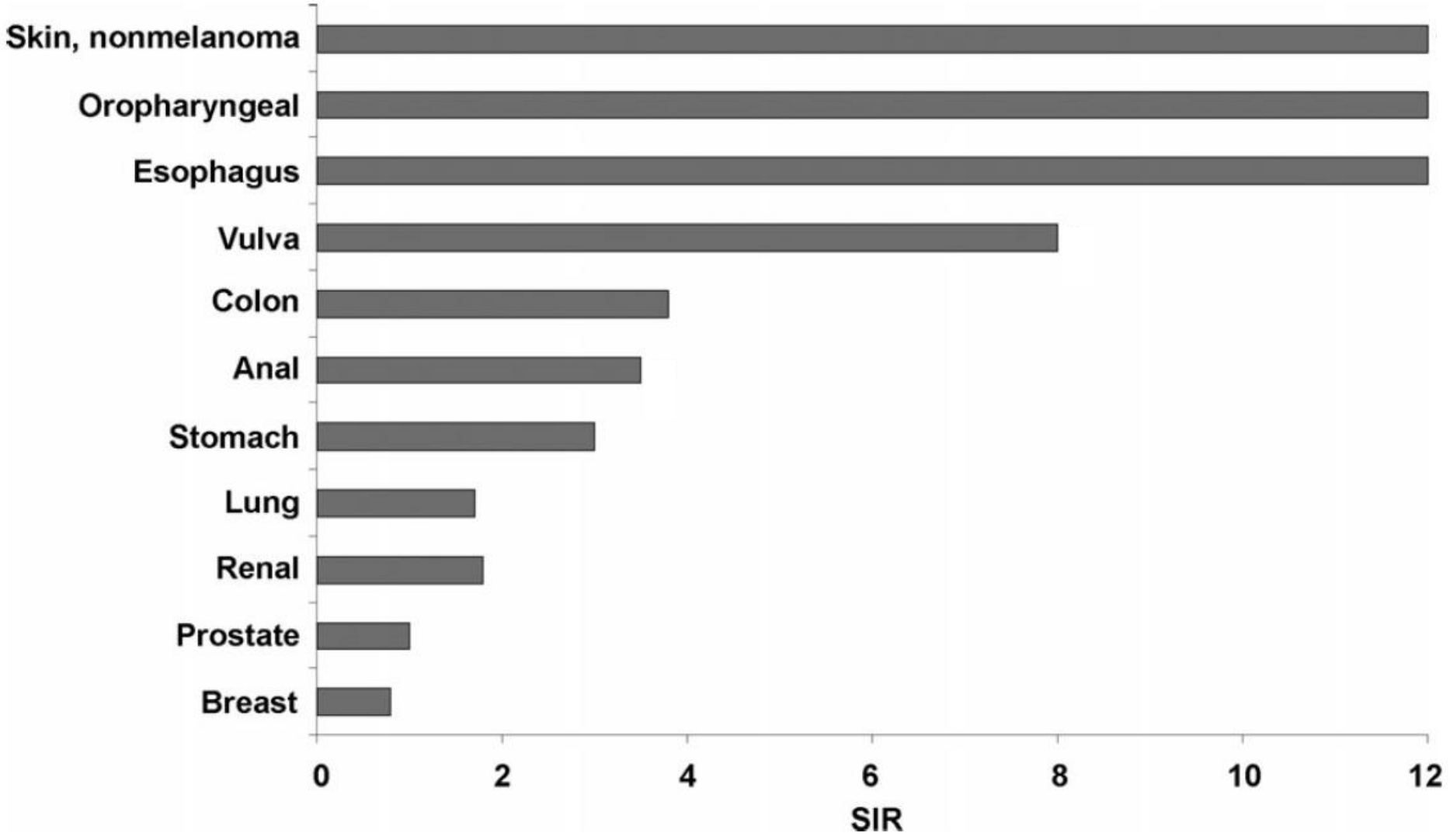
Tjon, Liver Transplantation, 2010

Incidentie t.o.v. algemene populatie



Chandok Liver Transpl 2012

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)

<u>Behandeling</u>

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

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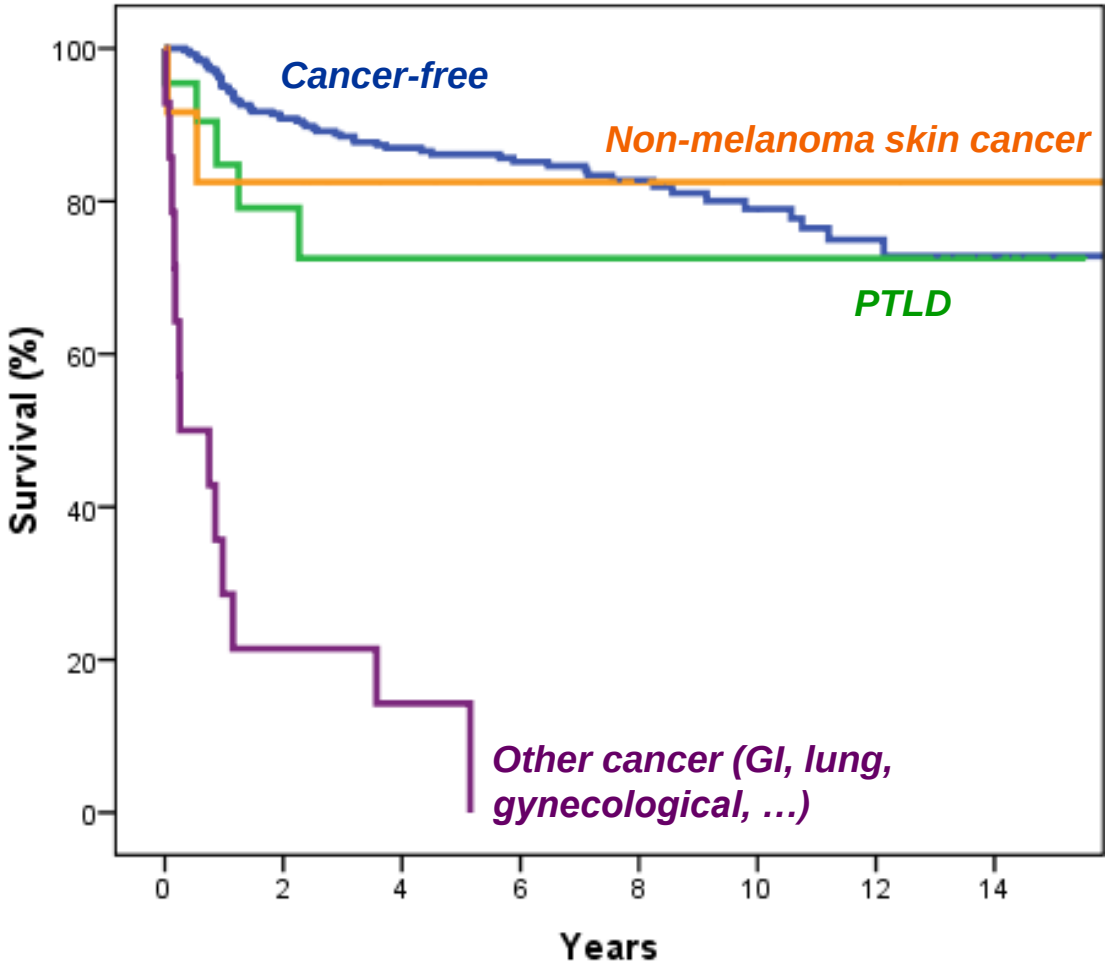
Effect van *de novo* kanker op overleving



Tjon et al, Liver Transplantation 2010

Terugkeer primaire leverziekte

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Terugkeer virale hepatitis

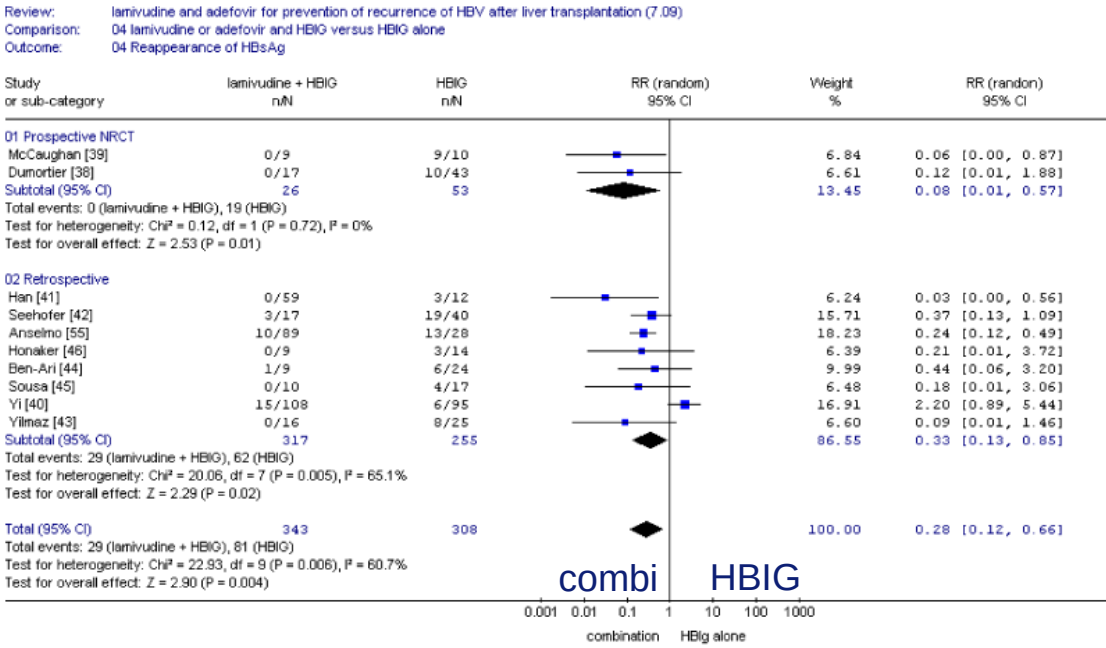
Universeel bij actieve infectie

HBV recurrence

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

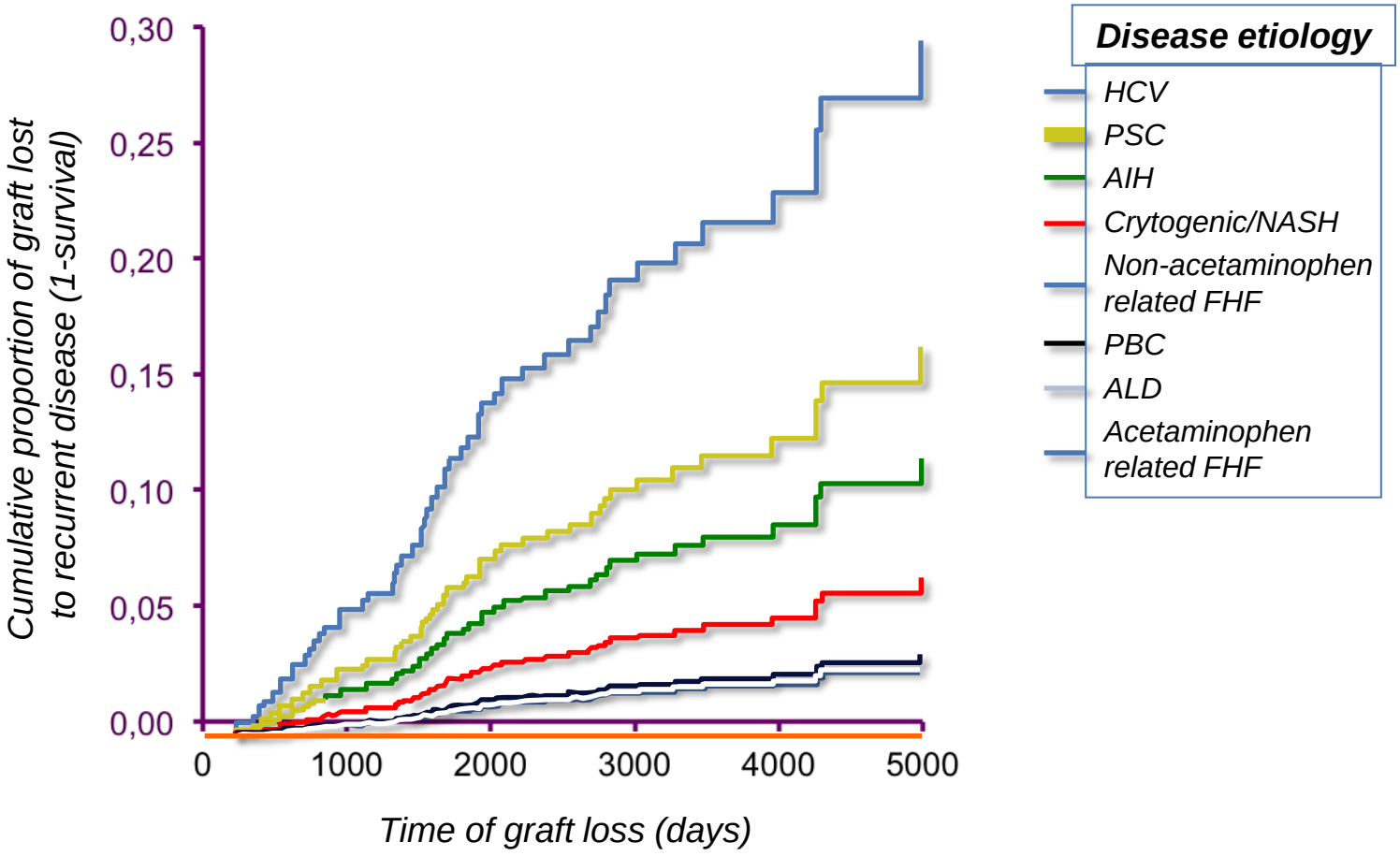
HCV recurrence

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



Katz et al. Transpl Infec Dis 2010; vd Meer J of Hepatology 2016

PSC is 2e 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.

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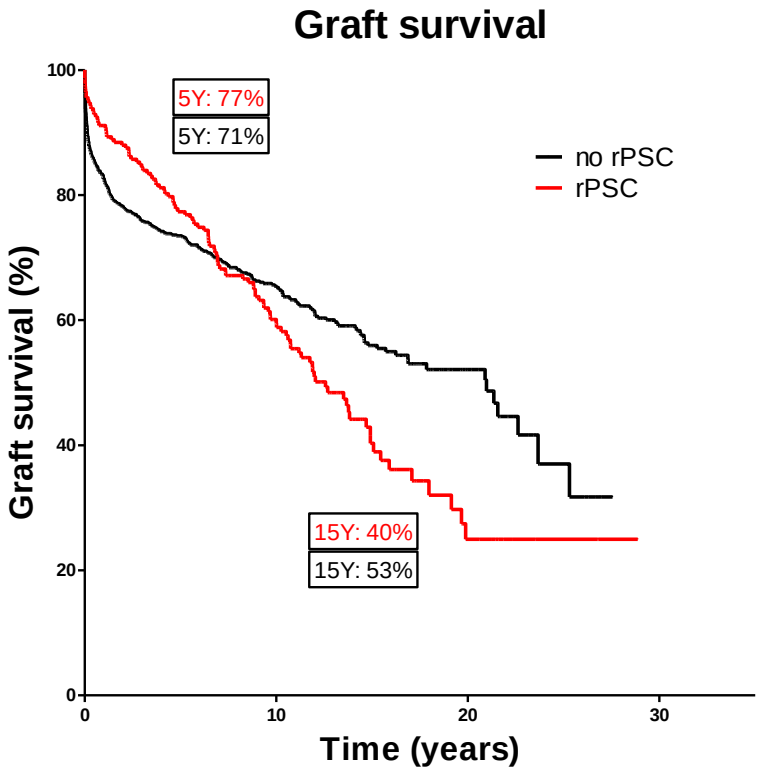
Recurrence PSC : impact op overleving

Incidentie rPSC 17.5%



	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*

Graft HR 4.01 (p< 0.001)

Patiënt HR 2.28 (p< 0.001)

Visseren et al. ILTS 2017

Osteoporose en wervelinzakking

Meeste botverlies 1e 3-6 m

Fractuur inc 1e jaar 20-30%

30-43% in cholestatische leverziekten

Hay J of Hepatology 2003

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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

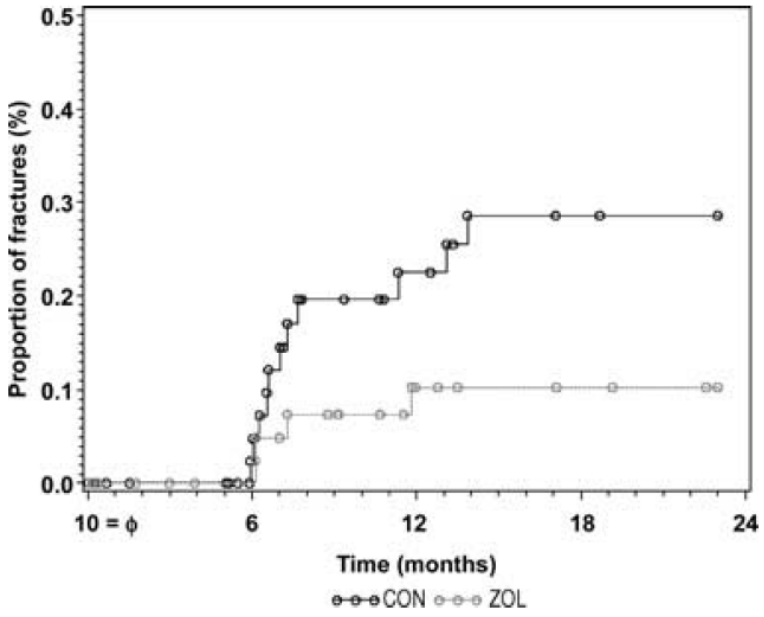

Figure 2: Primary study endpoint: fracture (log-rank test, p = 0.050).

Mells, Neuberger. Seminars in liver disease 2009
Bodinghauer, AJT, 2007

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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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