Selbsthilfe Organtransplantierter NRW
Beratung vor und nach Organtransplantationen

Heinrich Heine Universität Düsseldorf

Moderne, patientenadaptierte Immunsuppression 2019

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Department of Cardiovascular Surgery
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HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

UKD Universitätsklinikum Düsseldorf

Herz- und Gefäßzentrum

etwa 50 Jahre ändern viel…..

Moments in History

In December, 1967, a young woman, Denise Darvall, was walking across a street in Woodstock to buy a cake when a car struck her. She died in Groote Schuur Hospital and in doing so achieved immortality by becoming the world's first heart donor when Christiaan Neethling Barnard transferred her heart into the chest of Louis Washkansky.

Cape Town has been witness to many historic moments since the day Van Riebeeck anchored in Table Bay. Few, if any, brought more limelight to the city than the heart transplant. For the surgeon, Dr Barnard, soon to be a household name throughout the world, "the heart is merely a pump". But for those who equated the heart with love and death, the transplant seemed close to a miracle.

"Mr Louis Washkansky, the 55-year-old Cape Town man whose life is being sustained today by the heart of a dead 25-year-old woman after the world's first successful heart transplant yesterday, is conscious in Groote Schuur Hospital and in a satisfactory condition." Monday, 4th December 1967

Christian Barnaard, 3.12.1967

Irregularities

SPIEGEL

Veras Niere, Walters Geld

Süddeutsche.de Gesundheit

Transplantations-Skandal an Uni-Klinikum

Leber im Angebot

Von Christina Berndt

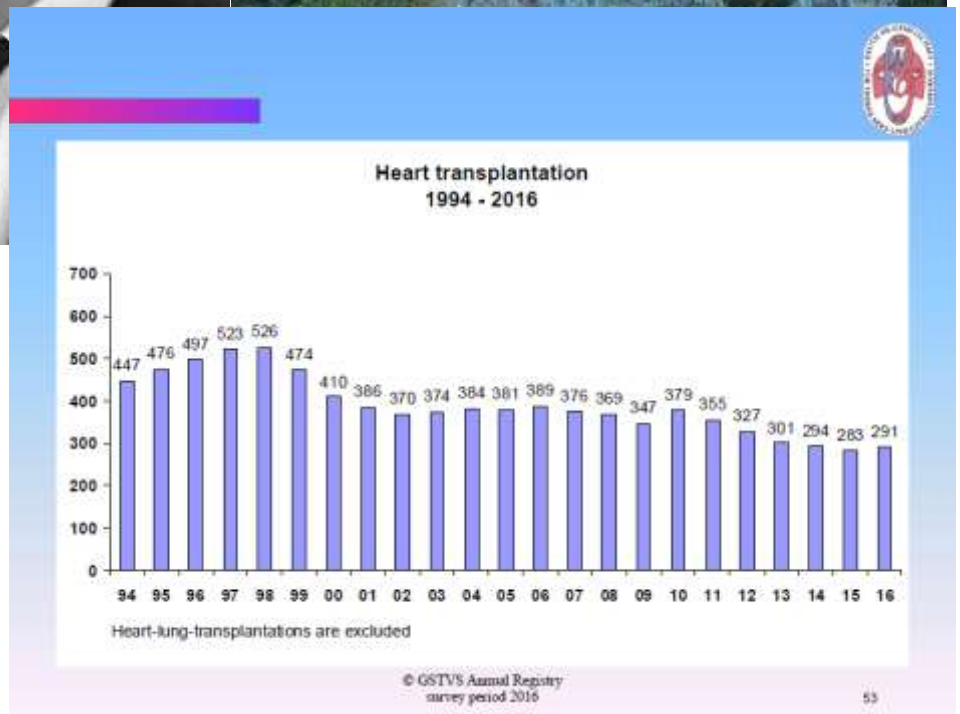
Neue Vorwürfe im Göttinger Transplantationsskandal

PANORAMA 55

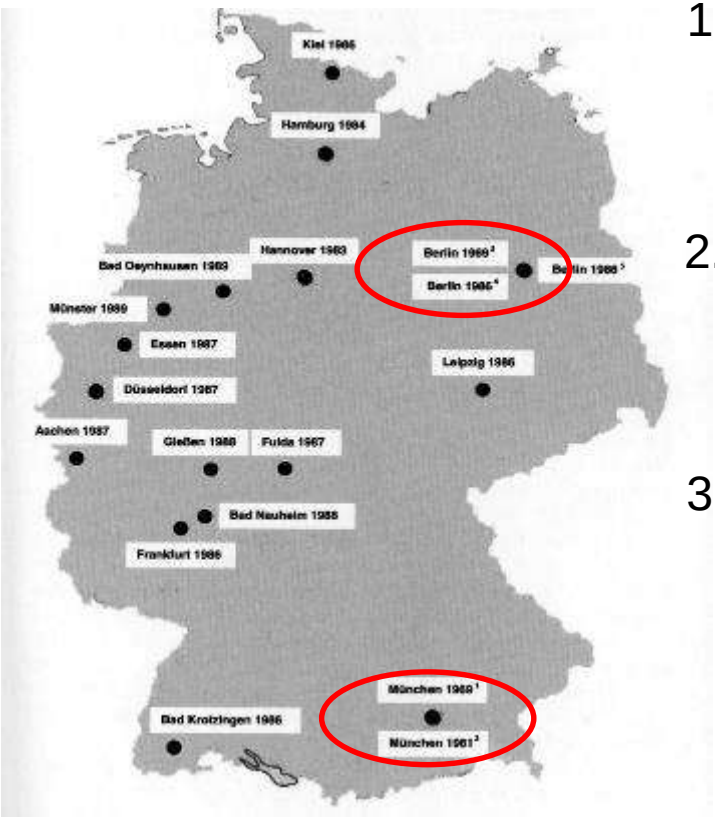
Organspende-Skandal: Die nächste Klinik unter Verdacht

Die Staatsanwaltschaft ermittelt jetzt auch in Regensburg. Chirurgie-Chef beurlaubt

Skandal um Organspende erfasst Bayern



HERZTRANSPLANTATION IN DEUTSCHLAND



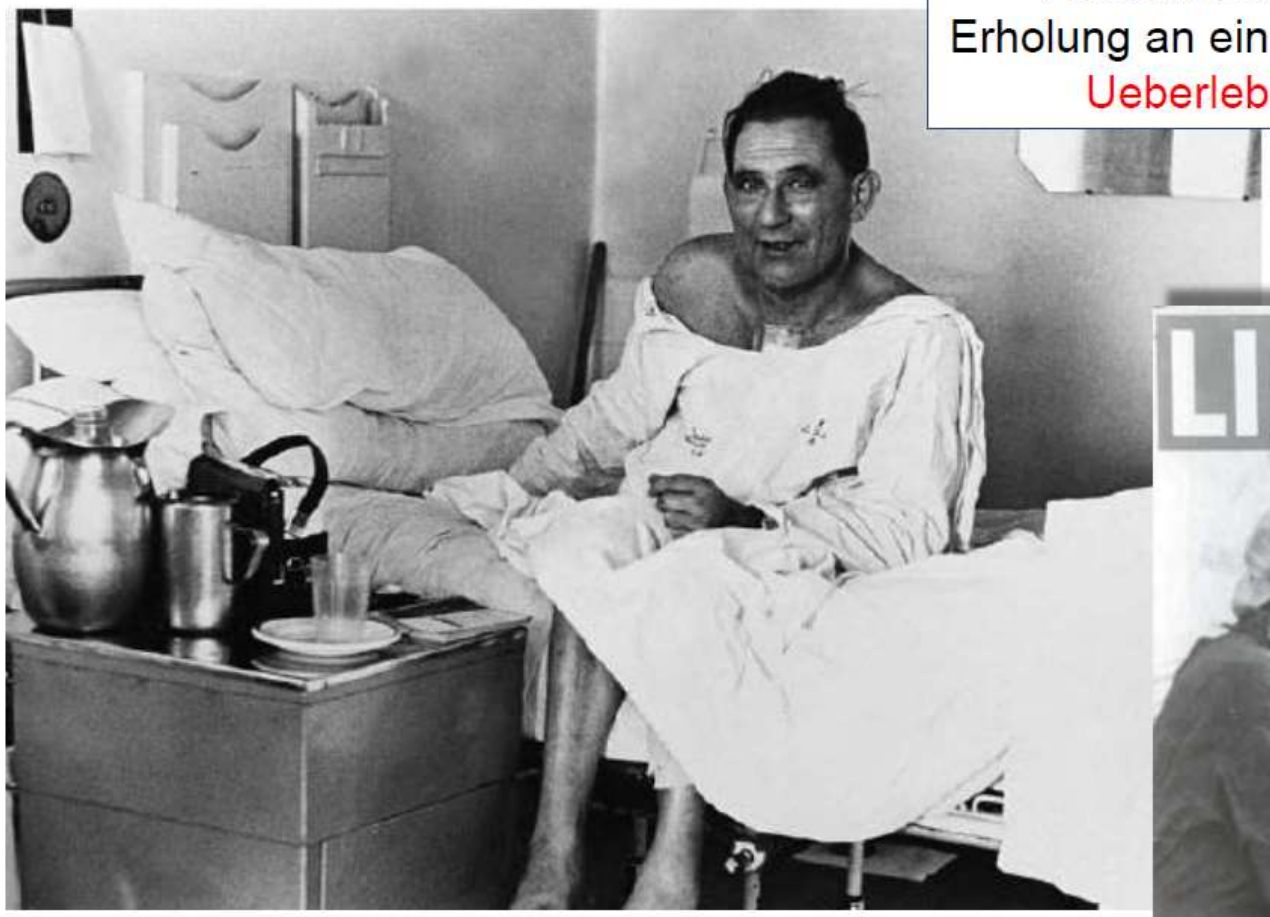
1. Fall : 13.02.1969 Prof. Sebening (München)

2. Fall : 03/1969 Prof. Sebening (München)

3. Fall : 11.07.1969 Prof. Bücherl (Berlin)

1. Herztransplantation am 03.12.1967
Louis Washkansky 57 Jahre

Verstarb nach zunaechst guter Erholung an einer Lungenentzuendung
Ueberlebenszeit: 18 Tage



HERZTRANSPLANTATION IN DEUTSCHLAND

1. Fall : 13.02.1969 Prof. Sebening (München)

➔ † nach 27 Std. im Rechtsherzversagen

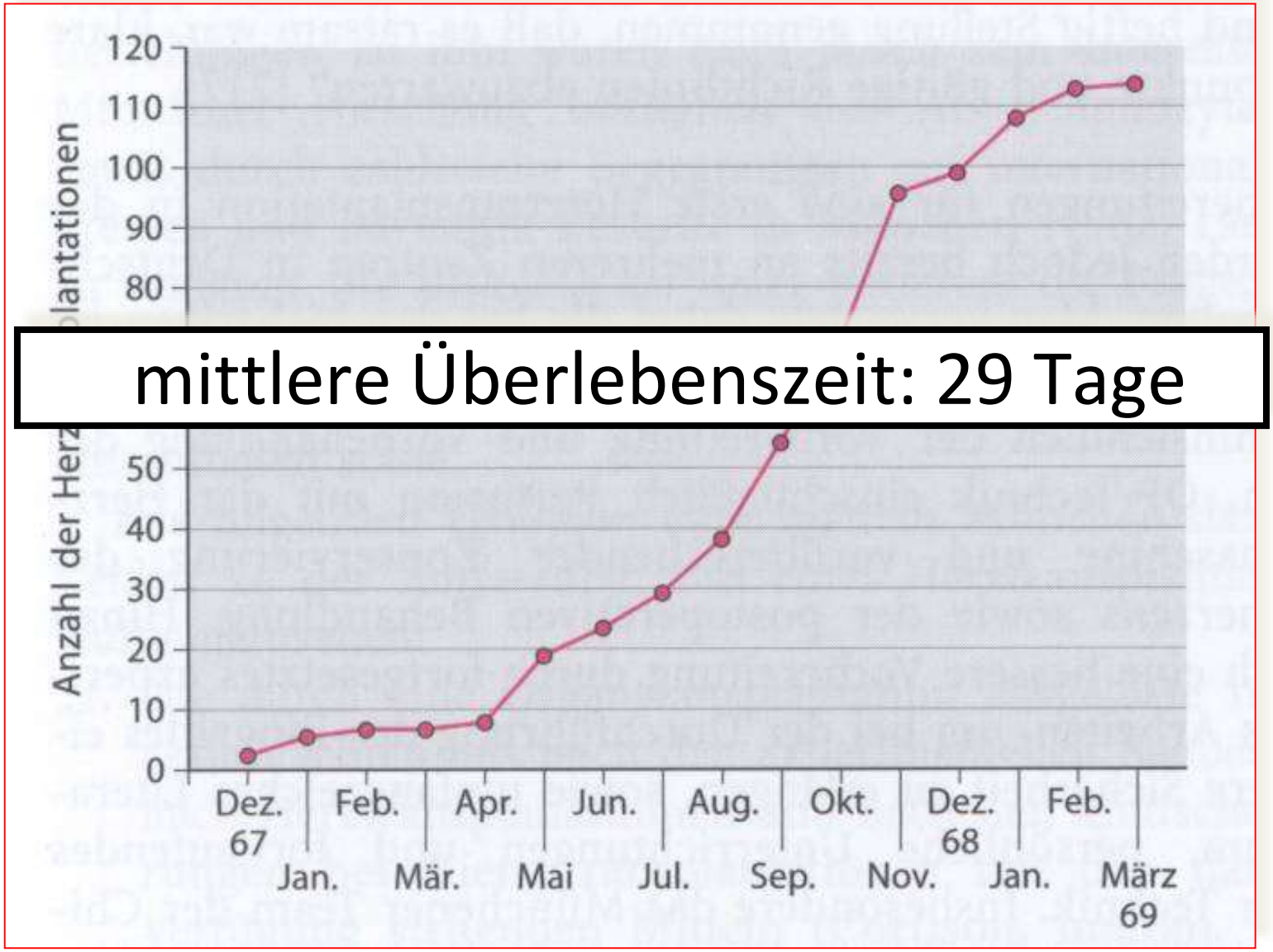
2. Fall : 03/1969 Prof. Sebening (München)

➔ † intraoperativ bei primärem Graftversagen

3. Fall : 11.07.1969 Prof. Bücherl (Berlin)

➔ † intraoperativ an einer Blutung

Anzahl der Herztransplantationen weltweit (nach 03.12.1967 bis 03.1969)



mittlere Überlebenszeit: 29 Tage

1971

….10 HTX

20.Juli 1969

1969

2019

Mondlandung: 4 Kilobyte Arbeitsspeicher brachten die ersten Menschen sicher auf den Erdtrabanten

min. 32 Gigabyte RAM

Entwicklung der Immunsuppression

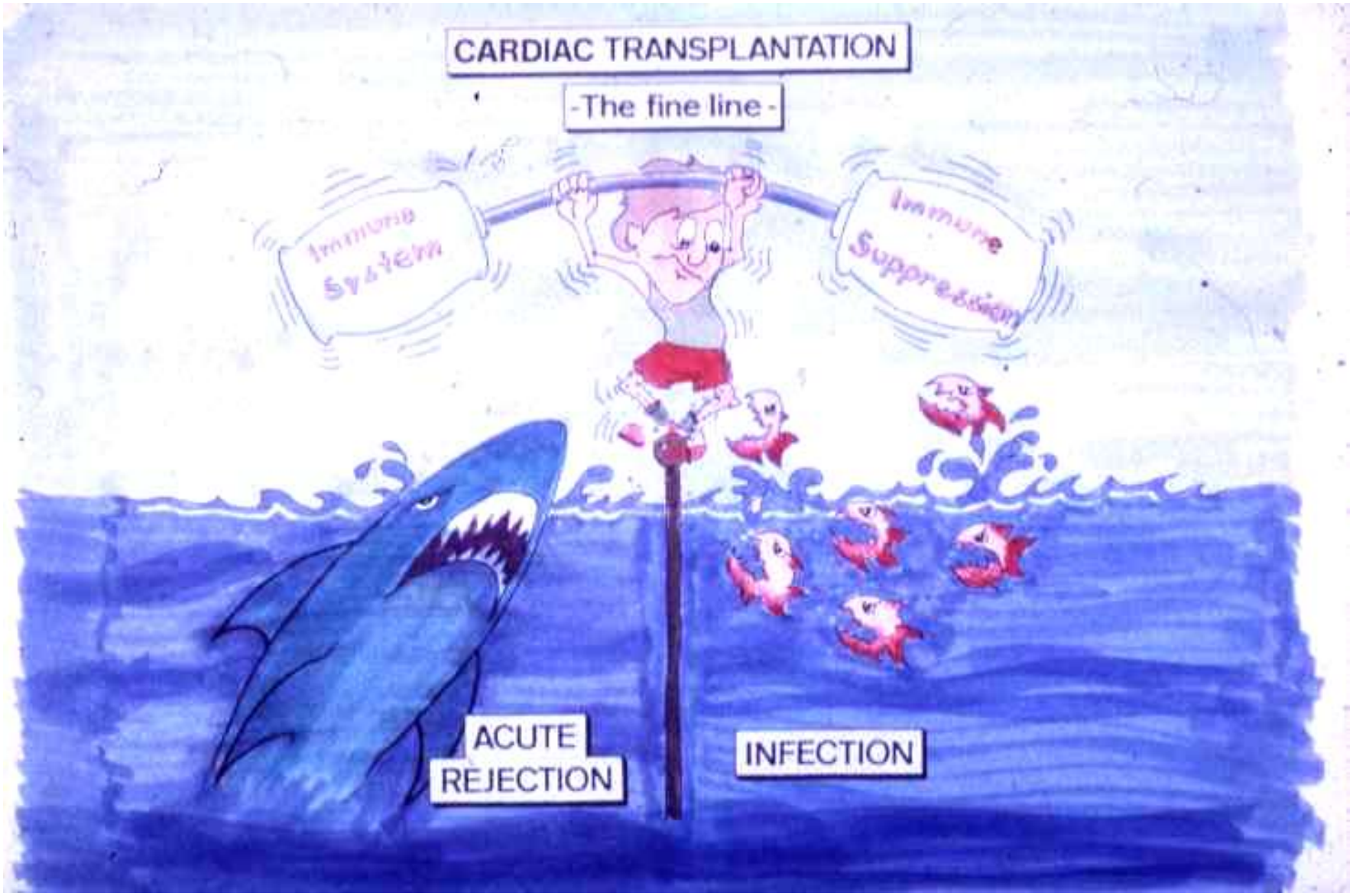
1959	Ganzkörperbestrahlung
1960 – 1962	6-Mercaptopurin und Azathioprin
1960 – 1965	zusätzlich myelotoxische Medikamente
1962 – 1963	systematischer Gebrauch von Cortison
1966	Lymphocytotoxische Sera/Antikörper
1978	Cyclosporin A
1989	Tacrolimus
1997	Mycophenolat mofetil
1998	Sirolimus
2004	Everolimus

„4 Kilobyte“

3.12.1967

„32 Gigabyte“

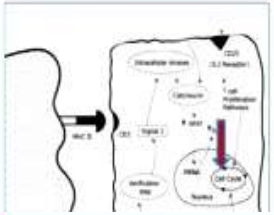
Ein schmaler Grat …..



Evolution of Immunosuppression

1959: Azathioprine

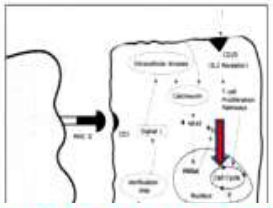
- Inhibits DNA synthesis
- CD28 down regulated
- Anaemia, leukopenia



Evolution of Immunosuppression

1961: Steroids

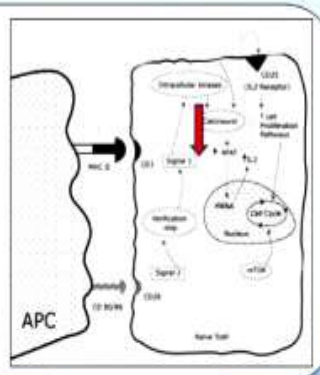
- Binds DNA
- Glucocorticoids regulate 20% leukocyte genes
- Multiple side-effects



Evolution of Immunosuppression

1994: Tacrolimus

- Japan: Streptomyces
- Calcineurin Inhibitor
- Capsules, granules, SR
- Diabetes
- Typical dose 1-4 mg bd (poymorphisms)
- Therapeutic levels 5-12 µ/l
- Cost US$ 200/month

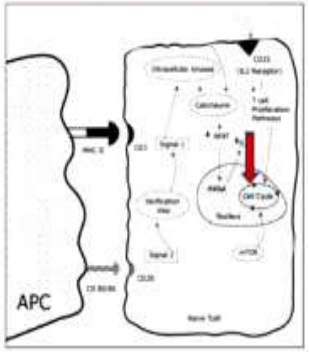


Calcineurin Inhibitor

Evolution of Immunosuppression

1997: MMF

- Inhibits DNA synthesis
- GI symptoms
- Anaemia, leukopenia
- Dose 600 mg/m^2
- Assays available
- US$ 250/month



- Levels 50-250 µ/l
- Cost US$ 200/month

Calcineurin Inhibitor

REVIEW

Personalized treatment in heart transplantation

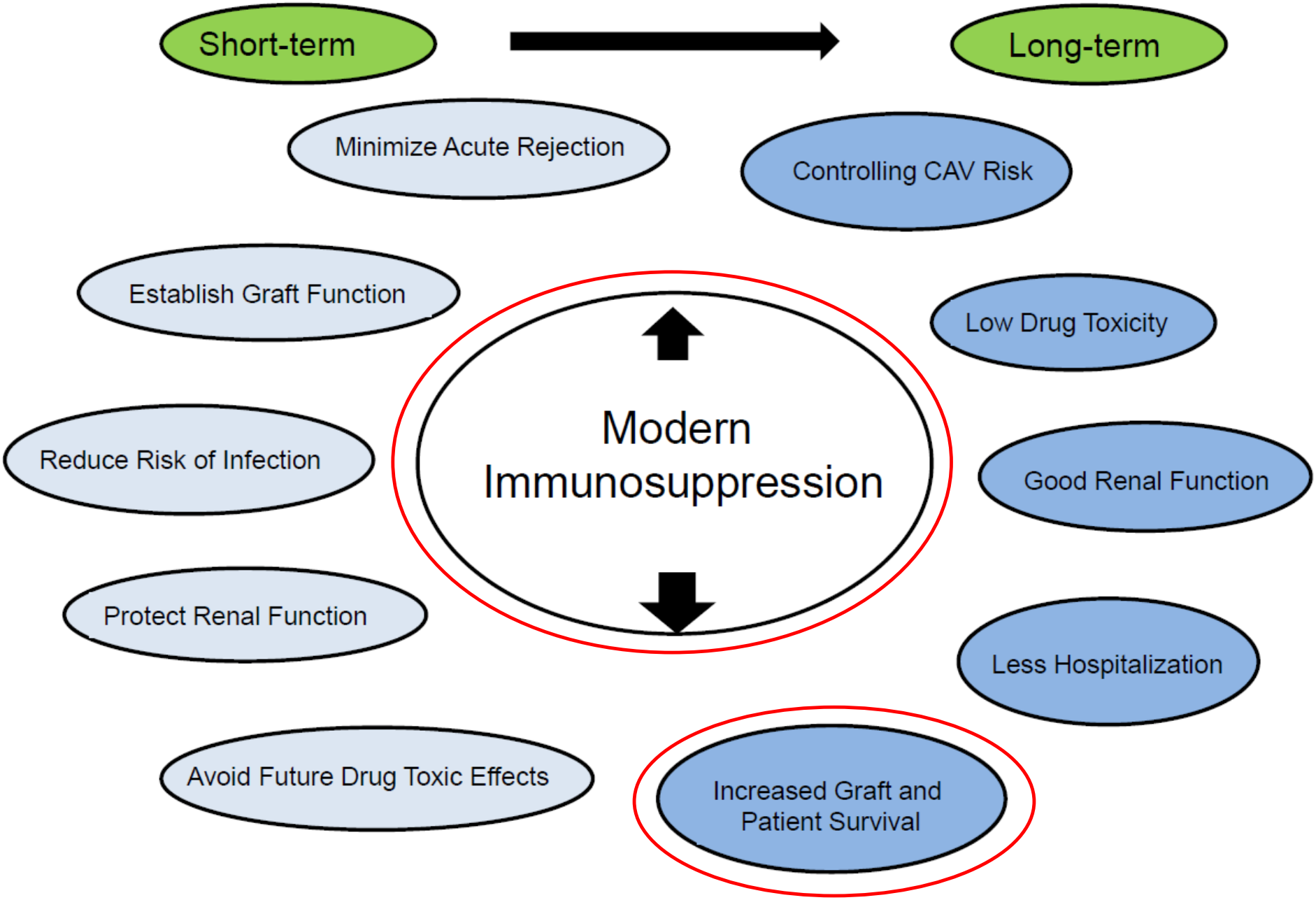
Kiran K. Khush

Purpose of review
We are entering the era of personalized medicine, in which pharmacogenomics and biomarker-based assays can be used to tailor diagnostic tests and drug therapies to individual patients. This new approach to patient-specific care offers the potential to maximize the efficacy of available medical treatments while reducing the incidence of adverse side effects. Here, we present approaches to personalize the care of heart transplant recipients.

Recent findings
Four strategies for personalized posttransplant care are described, including use of pharmacogenomic data to individualize the use of immunosuppressive drugs, immune monitoring to prevent acute rejection while reducing the long-term consequences of over immunosuppression, noninvasive surveillance for acute rejection, and targeted prophylaxis against opportunistic infections.

Summary
The long-term survival of heart transplant recipients is limited by side effects of immunosuppressive drugs, including infectious complications, renal dysfunction, and malignancy. We discuss strategies to maximize the benefits of immunosuppressive and prophylactic therapies while minimizing their long-term toxicities.

Keywords
cell-free DNA, gene expression profiling, heart transplantation, immune monitoring, pharmacogenomics



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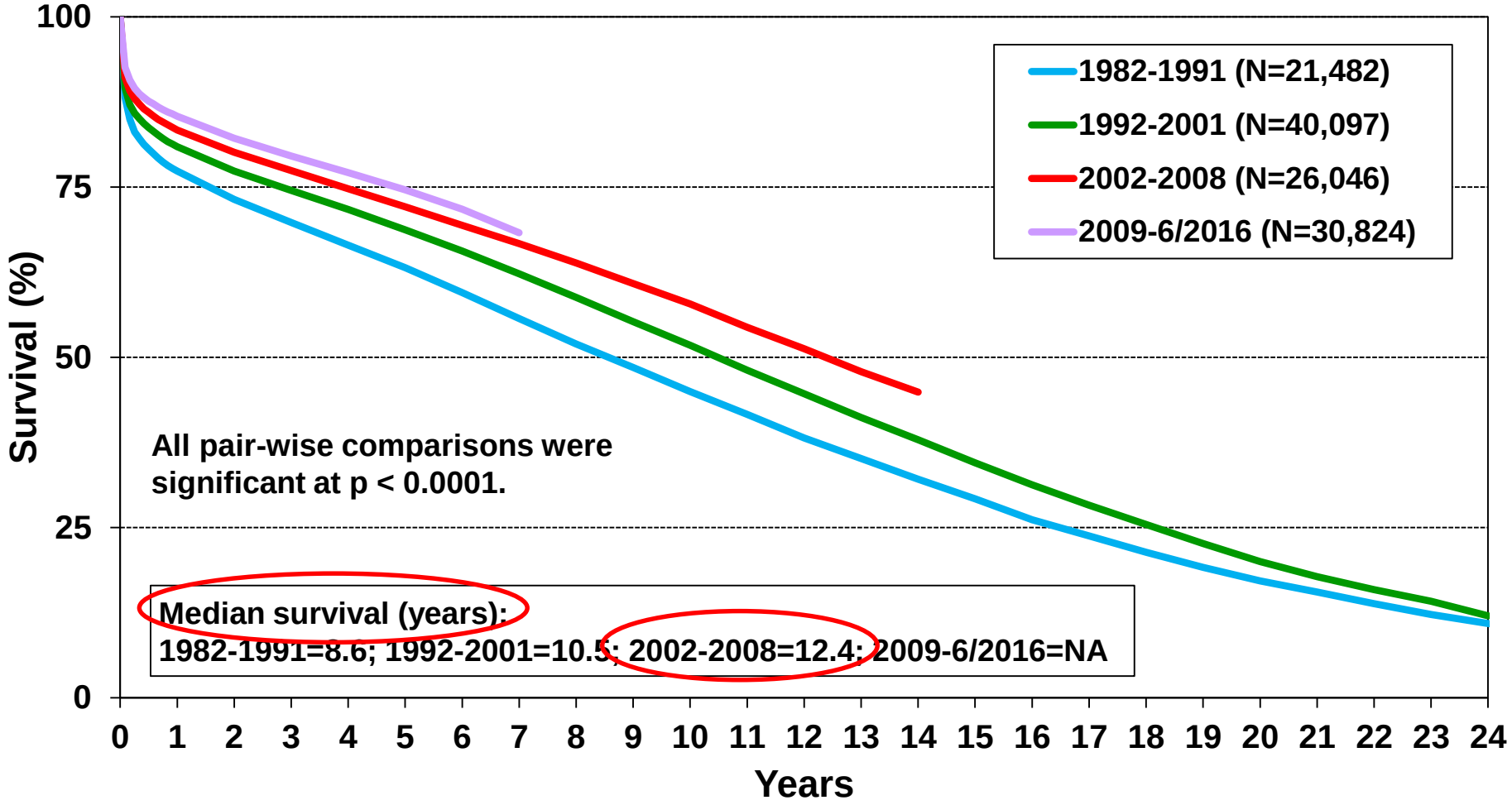
Adult Heart Transplants
Kaplan-Meier Survival by Era
(Transplants: January 1982 – June 2016)



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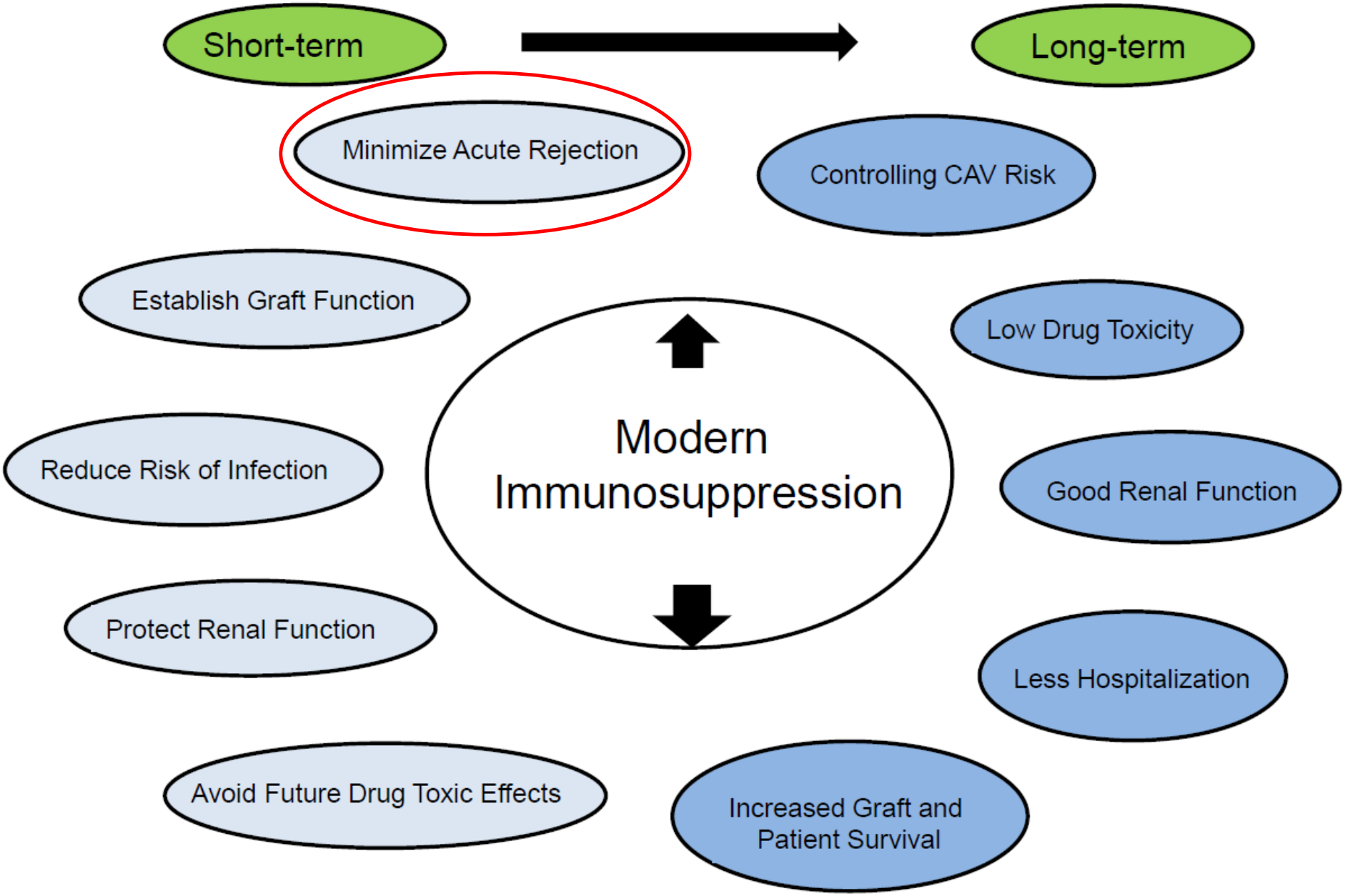
2018
JHLT. 2018 Oct; 37(10): 1155-1206



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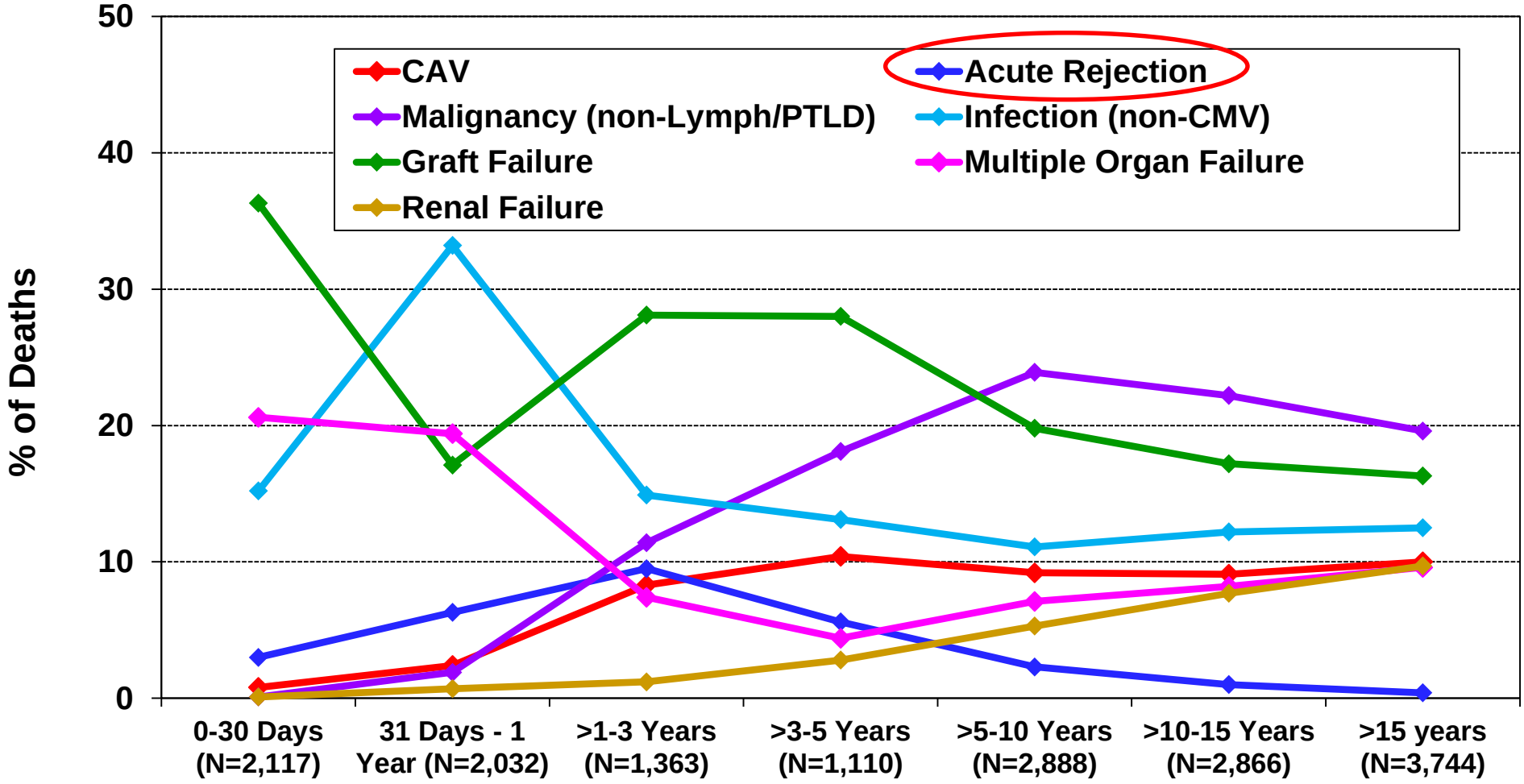
Adult Heart Transplants

Relative Incidence of Leading Causes of Death

(Deaths: January 2009 – June 2017)



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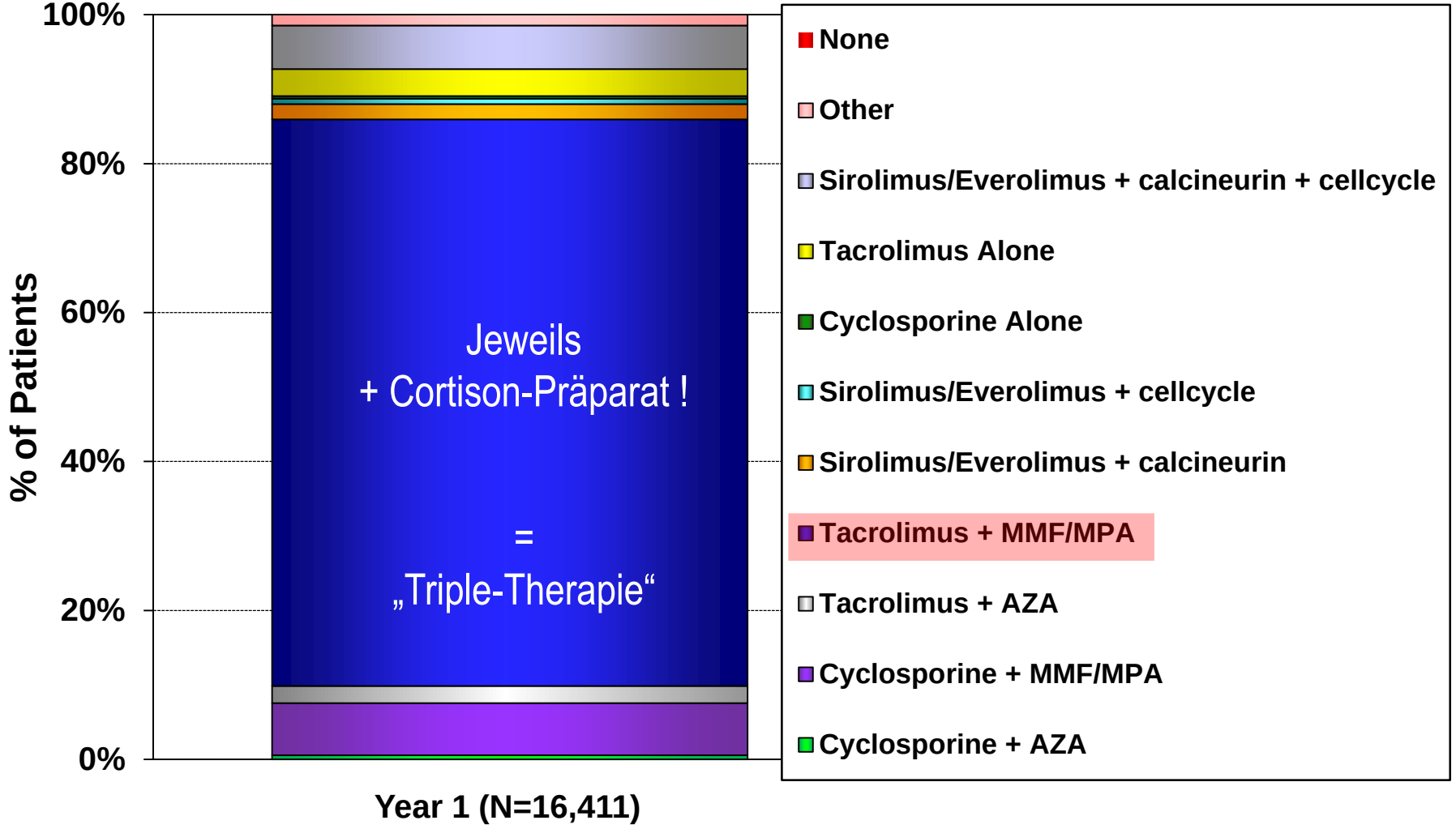
JHLT. 2018 Oct; 37(10): 1155-1206

Since only leading causes of death are shown, the sum of percentages for each time period is less than 100%.

Adult Heart Transplants
Maintenance Immunosuppression Drug Combinations at Time of 1 Year Follow-up (Follow-ups: January 2009 – June 2017)



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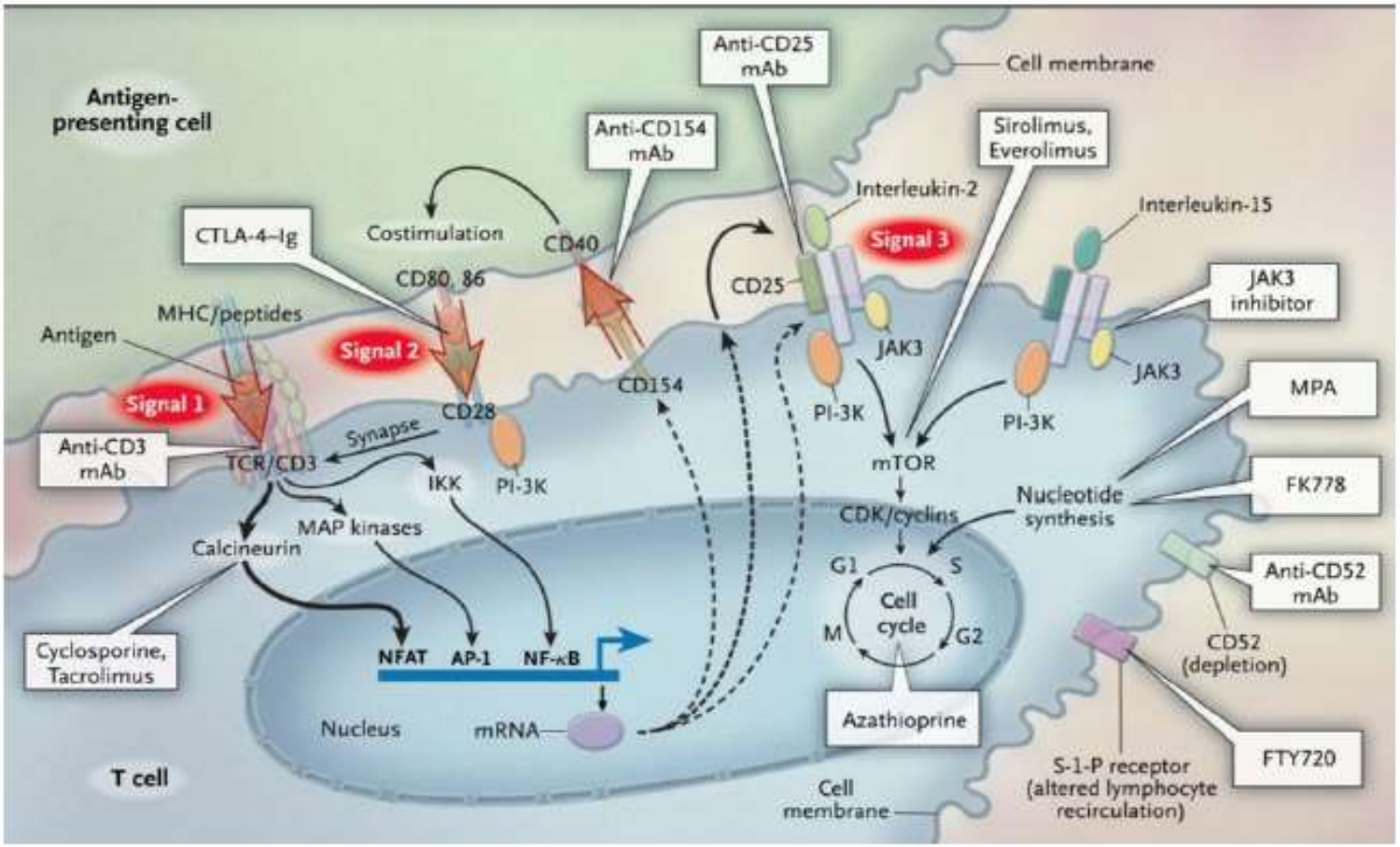
2018
JHLT. 2018 Oct; 37(10): 1155-1206

Analysis is limited to patients who were alive at the time of the follow-up.

Immunsuppression – Wirkung „3-Signal- Modell“

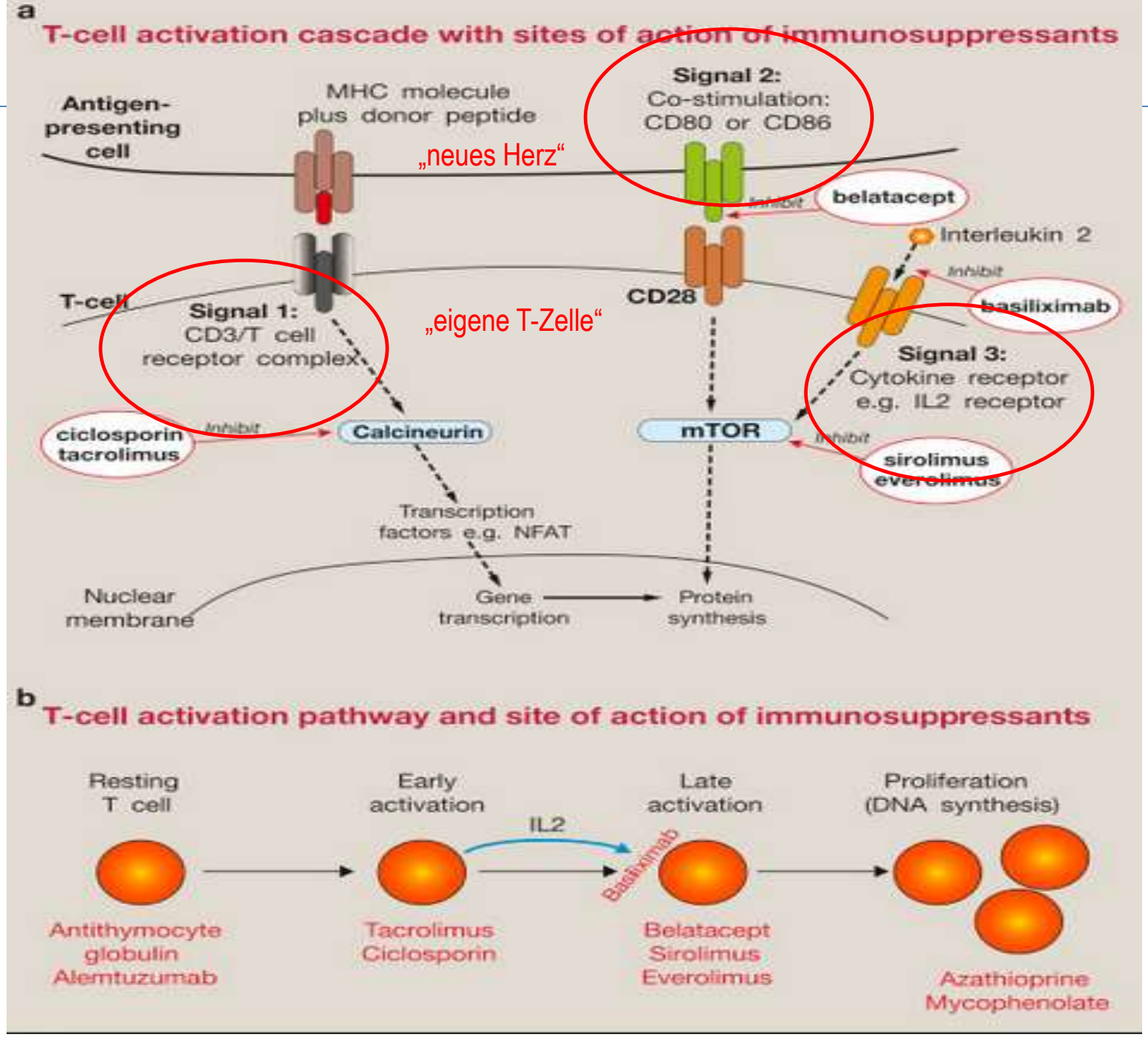
Figure. Individual Immunosuppressive Drugs and Sites of Action in the 3-Signal Model[1]



Anti-CD154 antibody has been withdrawn from clinical trials but remains of interest. FTY720 engagement of S-1-P receptors triggers and internalizes the receptors and alters lymphocyte recirculation, causing lymphopenia. Antagonists of chemokine receptors (not shown) are also being developed in preclinical models.

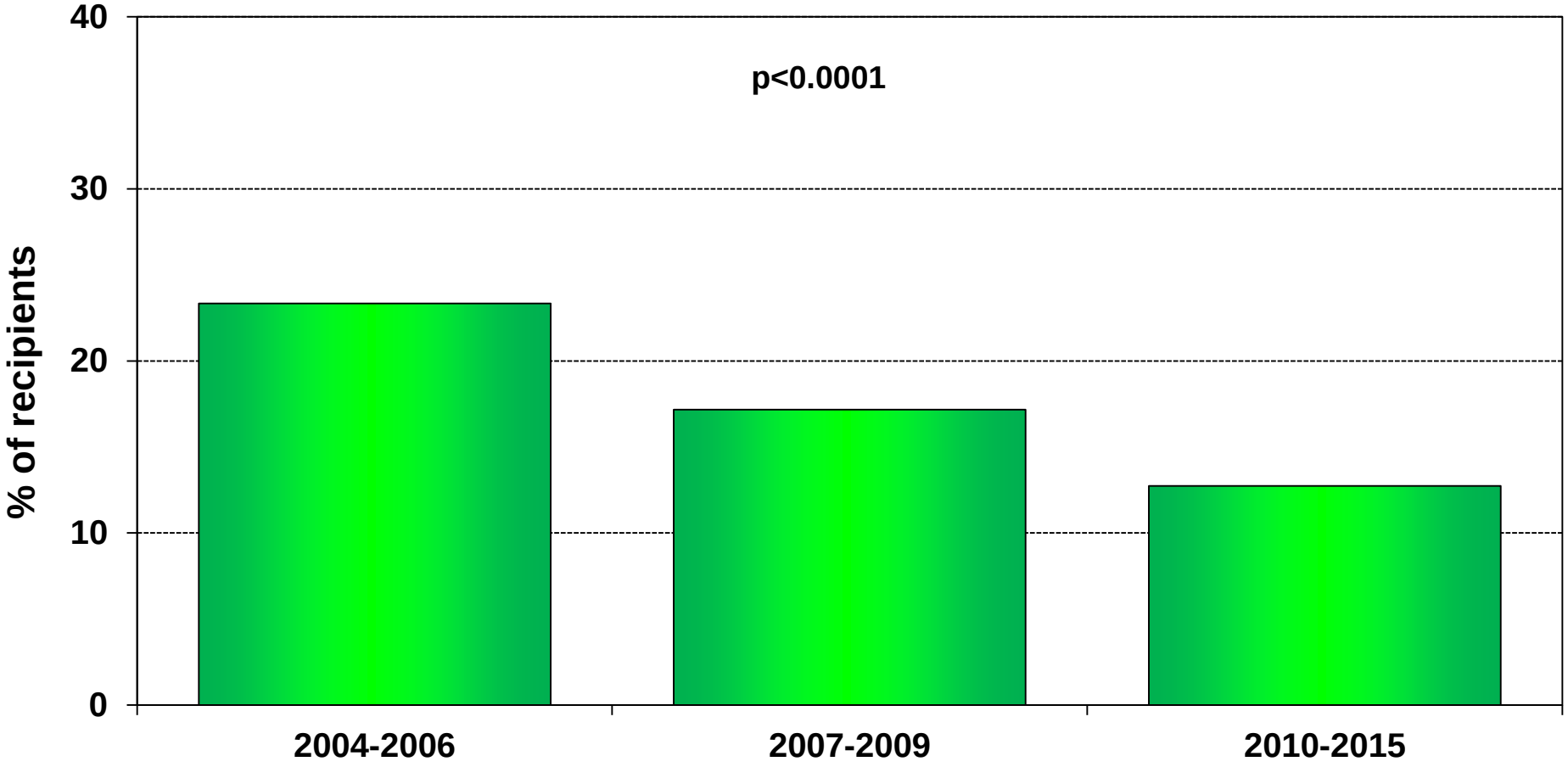
AP-1 indicates activating protein 1; CD, cluster of differentiation; CDK, cyclin-dependent kinase; CTLA-4–Ig, cytotoxic T-lymphocyte-associated protein 4 immunoglobulin; G1, gap 1; G2, gap 2; IKK, inhibitor of nuclear factor κB kinase; JAK3, Janus kinase 3; M, mitosis; mAb, monoclonal antibody; MAP, mitogen-activated protein; MPA, mycophenolic acid; mRNA, messenger ribonucleic acid; mTOR, molecular target of rapamycin; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor-κB; PI-3K, phosphoinositide-3-kinase; S, synthesis; S-1-P, sphingosine-1-phosphate; TCR, T-cell receptor.

From Halloran PF. Immunosuppressive drugs for kidney transplantation. *N Engl J Med.* 2004;351(26):2715-2729.


a
T-cell activation cascade with sites of action of immunosuppressants
Antigen-presenting cell
MHC molecule plus donor peptide
Signal 2: Co-stimulation: CD80 or CD86
„neues Herz“
Inhibit
belatacept
Interleukin 2
Inhibit
basiliximab
T-cell
Signal 1: CD3/T cell receptor complex
„eigene T-Zelle“
CD28
Signal 3: Cytokine receptor e.g. IL2 receptor
ciclosporin tacrolimus
Inhibit
Calcineurin
mTOR
Inhibit
sirolimus everolimus
Transcription factors e.g. NFAT
Nuclear membrane
Gene transcription
Protein synthesis
b
T-cell activation pathway and site of action of immunosuppressants
Resting T cell
Early activation
Late activation
Proliferation (DNA synthesis)
IL2
Basiliximab
Antithymocyte globulin
Alemtuzumab
Tacrolimus
Ciclosporin
Belatacept
Sirolimus
Everolimus
Azathioprine
Mycophenolate

Adult Heart Transplants

% of Recipients Experiencing *Treated* Rejection Between Transplant Discharge and 1-Year Follow-Up by Era



Analysis is limited to patients who were alive at the time of the follow-up.

Treated rejection = Recipient was reported to (1) have at least one acute rejection episode that was treated with an anti-rejection agent; or (2) have been hospitalized for rejection.

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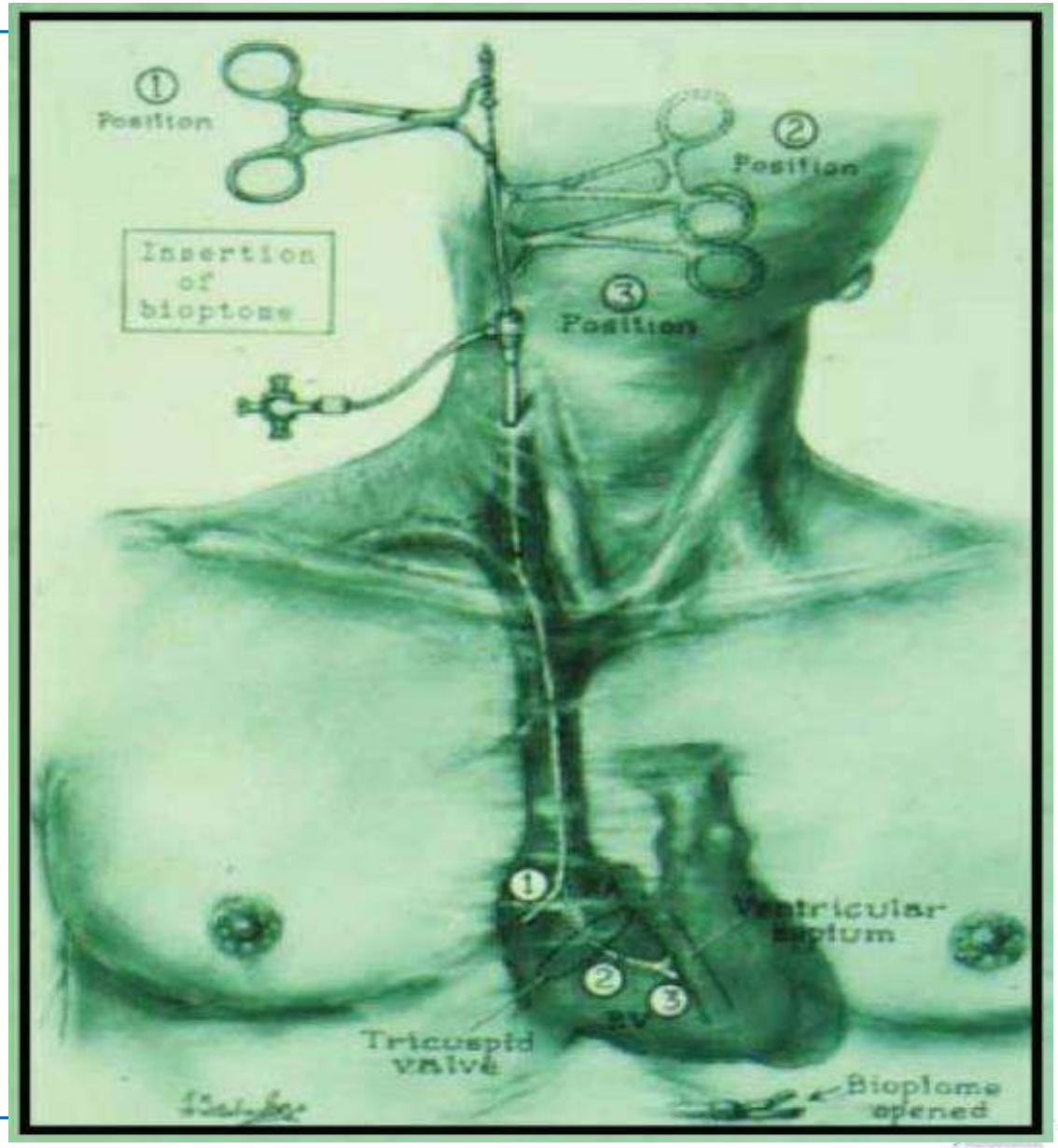
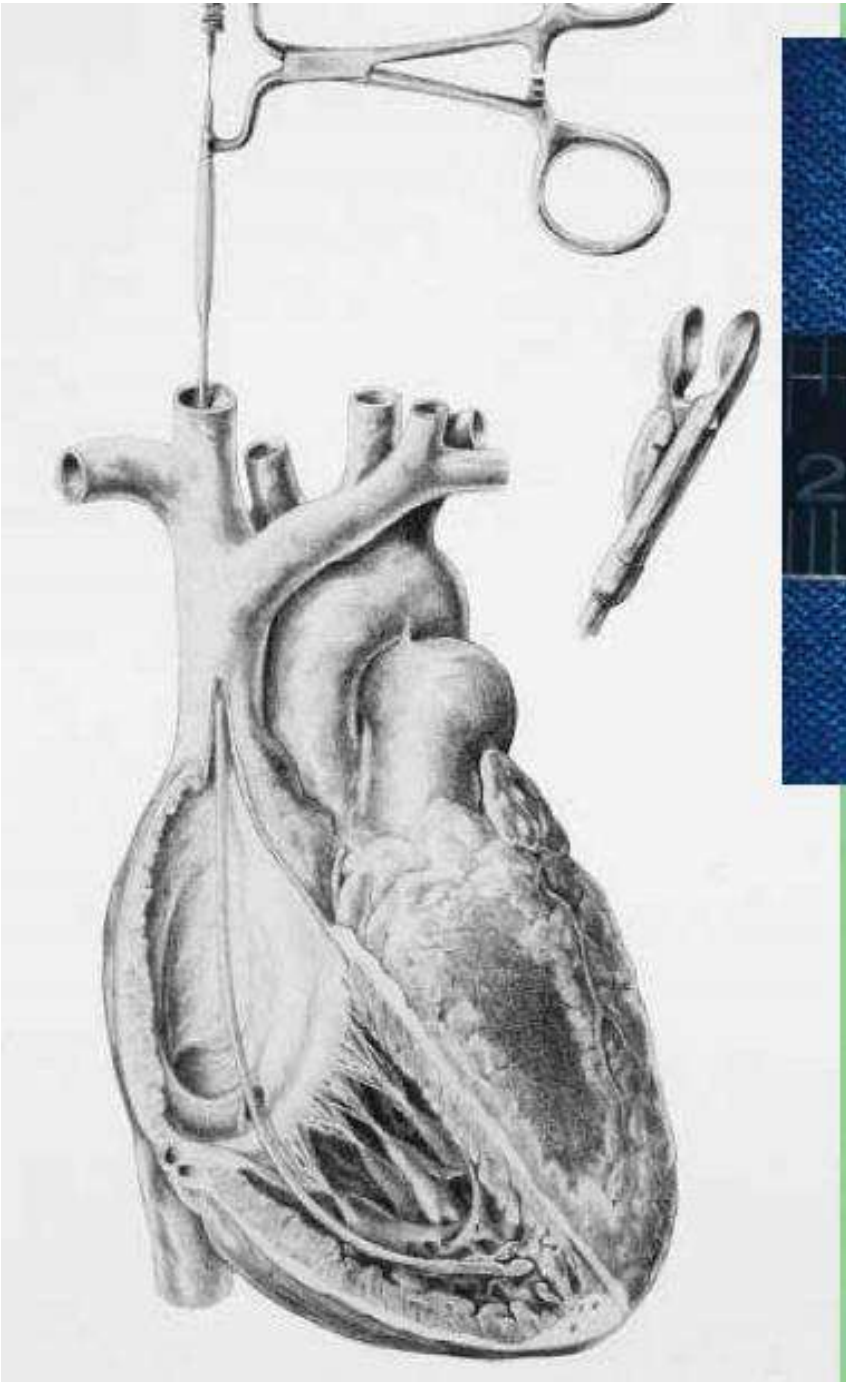
auch 2018 weiter Goldstandard der Diagnostik

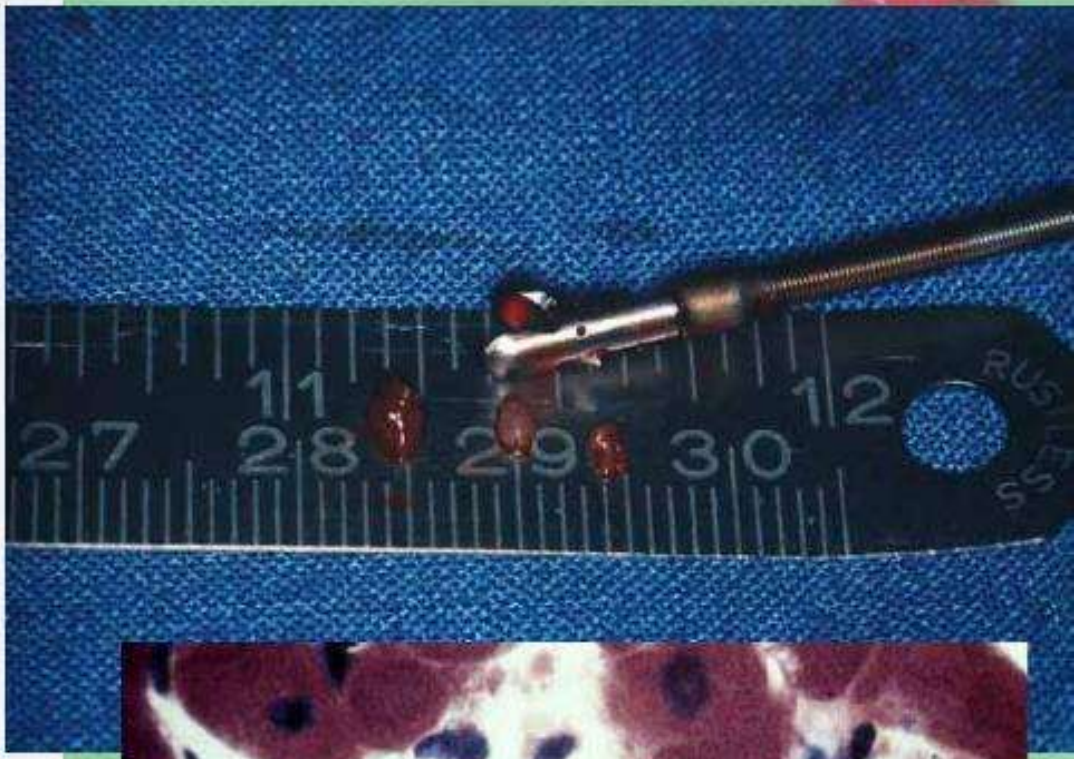
Herzzentrum Düsseldorf

EMB
=
Endomyokardbiopsie

Durchführung zunächst in wöchentlichen Abständen ab dem 7. postoperativen Tag



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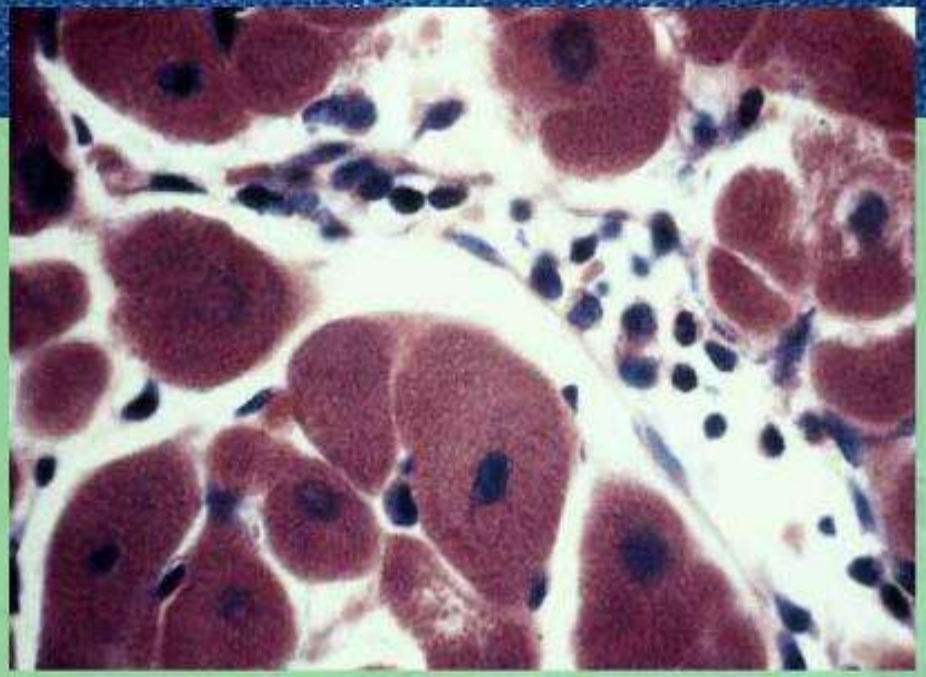
RUSTLESS



Einteilung nach ISHLT:

Alt:

(J. Heart Transplant **1990** , Nr. 9, 587-593)

Grade:

0 No rejection

1 A = Focal (Perivascular or interstitial) infiltrate without necrosis

B = Diffuse but spare infiltrate without necrosis

2 One focus only with aggressive infiltration an/ or focal myocyte damage

3 A = Multifocal aggressive infiltrates and /or myocyte damage

B = Diffuse inflammatory process with necrosis

4 Diffuse aggressive polymorphous +/- infiltrate +/- edema +/- hemorrhage +/- vasculitis with necrosis

Neu:

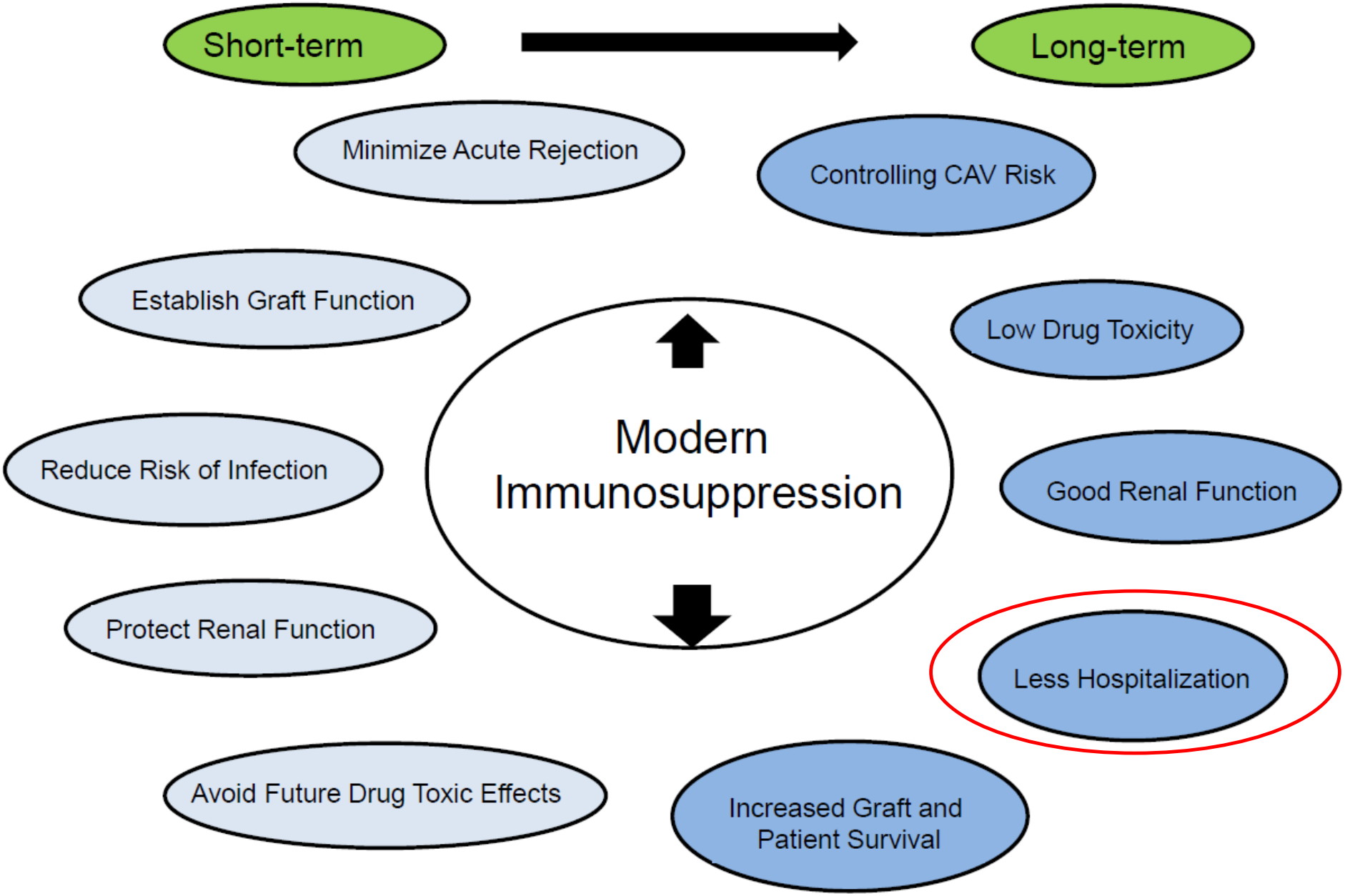
Revidierte Nomenklatur (ISHLT Consensus Report ; Stewart et al., **2005**):

0R Keine Abstoßungsreaktion (alt 0)

1R Leichte Abstoßungsreaktion (alt 1A, 1B, 2)

2R Mäßige / mittelgradige Abstoßungsreaktion (alt 3A)

3R Schwere Abstoßungsreaktion (alt 3B, 4)



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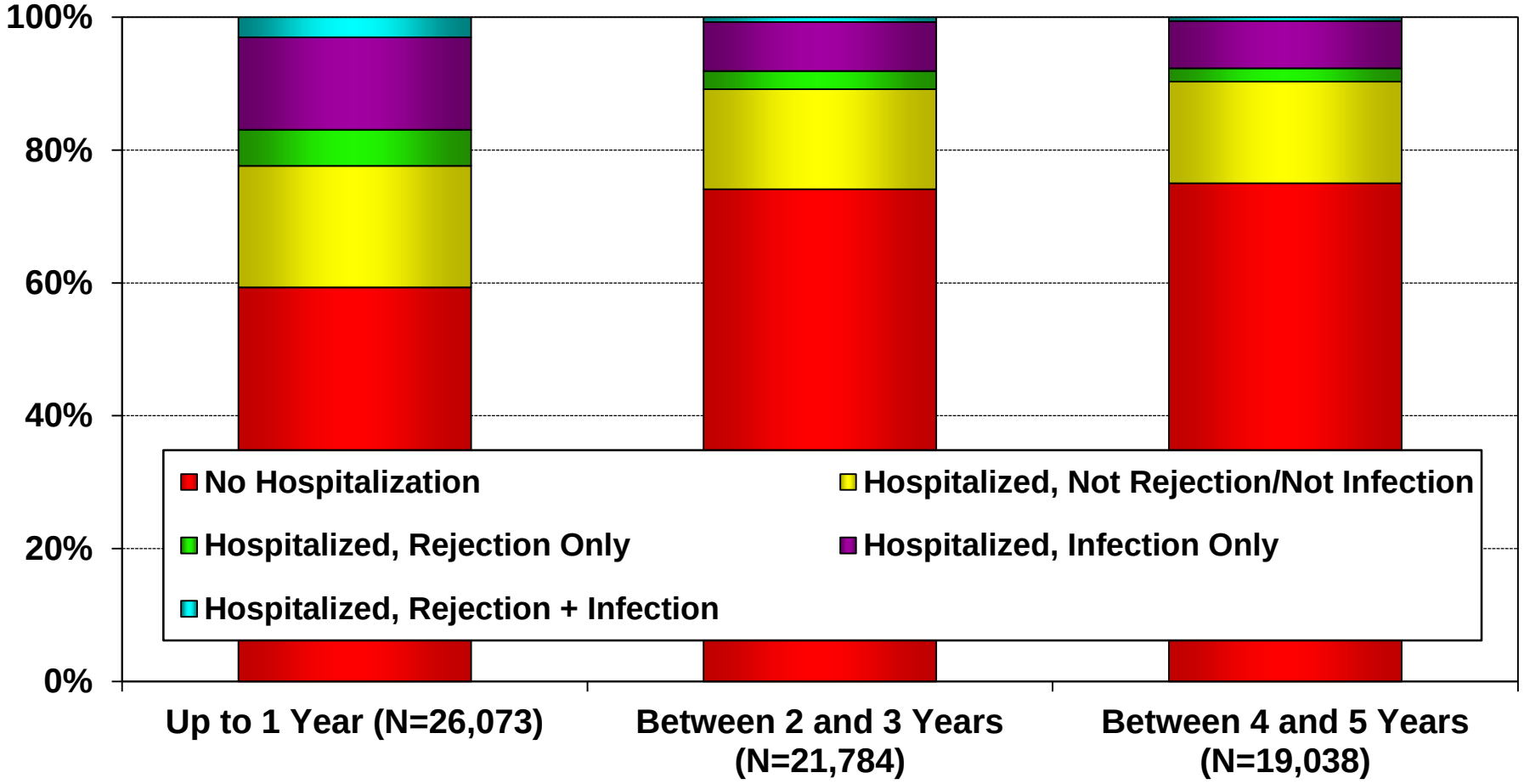
Krankenhaus-Aufnahmen nach HTX

Adult Heart Transplants

Rehospitalization Post Transplant of Surviving Recipients

(Follow-ups: January 2004 – June 2017)



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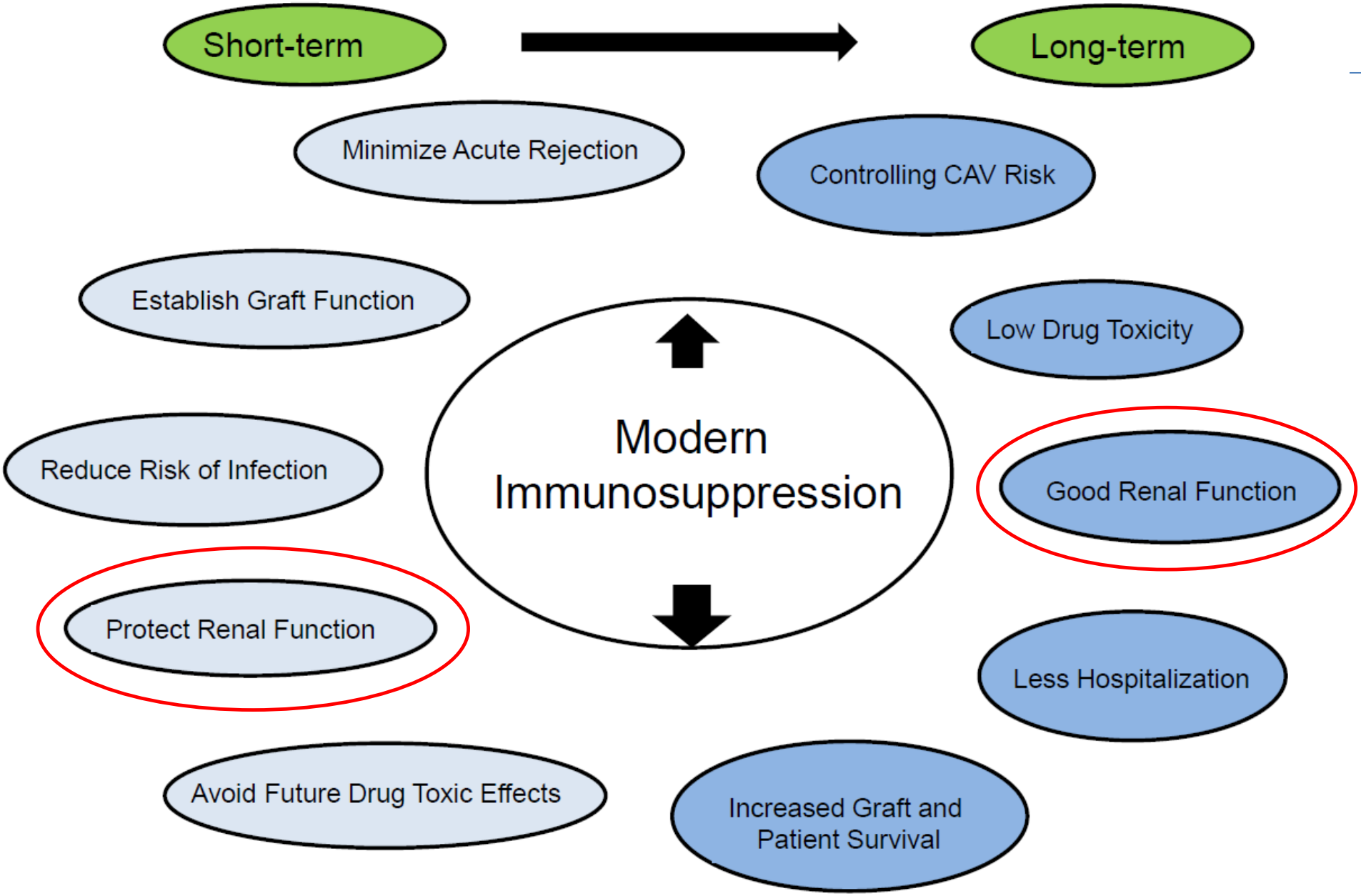

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Adult Heart Transplants

Cumulative Morbidity Rates in Survivors within 1, 5 and 10 Years Post Transplant (Transplants: January 1994 – June 2016)

Outcome	Within 1 Year	Total N with known response	Within 5 Years	Total N with known response	Within 10 Years	Total N with known response
Severe Renal Dysfunction[1]	6.9%	(N=38,588)	16.1%	(N=22,131)	23.1%	(N=9,000)
Creatinine > 2.5 mg/dl	*5.4%*		*12.7%*		*15.1%*	
Chronic Dialysis	*1.4%*		*2.9%*		*6.0%*	
Renal Transplant	*0.1%*		*0.6%*		*2.0%*	
Diabetes[2]	21.0%	(N=38,844)	34.5%	(N=22,396)	-	
Cardiac Allograft Vasculopathy	7.6%	(N=35,766)	29.2%	(N=16,921)	47.2%	(N=5,787)

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JHLT. 2018 Oct; 37(10): 1155-1206

[1] Severe renal dysfunction = Creatinine > 2.5 mg/dl (221 µmol/L), dialysis or renal transplant
[2] Data are not available 10 years post-transplant.

Nebenwirkungen der IS / CNI

Nebenwirkungen	CyA-ME	Tac	Aza	MMF	mTOR	Steroide	Belata-cept**
Funktionelle Verän-derungen der Niere	+++	++	-	-	- /+++*	-	-
Strukturelle Verän-derungen der Niere	++	+	-	-	++	-	-
Neurotoxizität (Tremor)	++	++	-	-	-	-	++
Diabetogener Effekt	++	++(+)	-	-	-	+++	
Gastrointestinale Störungen (Diarrhö)	++	++	+++	+++	+++	+	++
Hypertonie	++	+	-	-	-	++	-
Hyperlipidämie	++	+	-	-	+++	++	-
Hypertrichose	++	-	-	-	-	-	-
Gingivahyperplasie	++	-	-	-	-	-	-
Alopezie	-	+	-	-	-	-	-
Leukopenie	+	+	++	++	++	-	-
Thrombozytopenie	+	+	++	++	+++	-	-
Anämie	+	+	+	++	+++	-	-
Osteoporose	+	-	-	-	-	+++	-

CNI-Reduktion

REVIEW

Calcineurin-inhibitor minimization protocols in heart transplantation

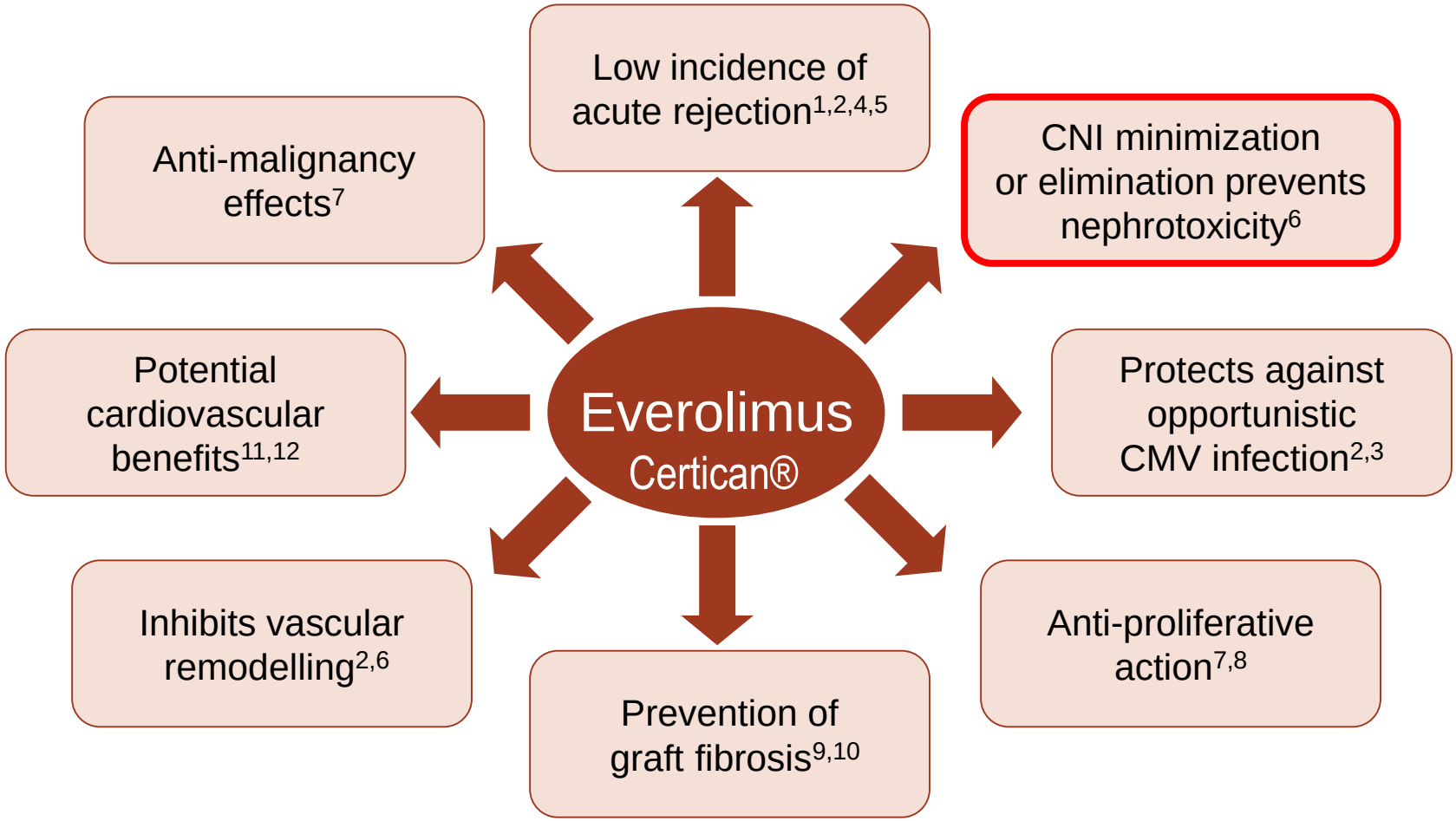
Andreas Oliver Zuckermann and Arezu Z. Aliabadi

Department of Cardiothoracic Surgery, Medical University of Vienna, Vienna, Austria

Journal compilation © 2008 European Society for Organ Transplantation **22** (2009) 78–89

In conclusion, CNI-delay, -minimization, and -elimination seem to be possible treatment options after cardiac transplantation, yet there is still a lack of prospective randomized trials confirming promising results of small single center experience. Nevertheless, these strategies bear huge potential to counteract the increasing problems and complications of long-term immunosuppression.

Everolimus: a multifaceted approach to help improve long-term outcomes



CNI, calcineurin inhibitor; CMV, cytomegalovirus

1. Pascual J. *Transplantation* 2005;79(Suppl 9):S76–S79; 2. Eisen H *et al. N Engl J Med* 2003;349:847–58; 3. Vitko S *et al. Am J Transplant* 2005;5:2521–30; 4. Tedesco-Silva H *et al. Transpl Int* 2007;20:27–36; 5. Nashan B *et al. Transplantation* 2004;78:1332–40; 6. Nashan B. *Transplant Proc* 2001;33:3215–20; 7. Majewski M *et al*. *Transplantation* 2003;75:1710–7; 8. Schuler W *et al. Transplantation* 1997;64:36–42; 9. Viklicky O *et al. Transplantation* 2000;96:497–502; 10. Koch M *et al. Transplantation* 2007;83:498–505; 11. Andrés V *et al. Nephrol Dial Transplant* 2006;21(Suppl 3):iii14–7; 12. Pascual J *et al. Nephrol Dial Transplant* 2006;21(Suppl 3):iii38–41

Transplant International

ORIGINAL ARTICLE

Long-term outcomes of thoracic transplant recipients following conversion to everolimus with reduced calcineurin inhibitor in a multicenter, open-label, randomized trial

Lars Gullestad[1,2], Hans Eiskjaer[3], Finn Gustafsson[4], Gerdt C. Riise[5], Kristjan Karason[6], Göran Dellgren[6], Göran Rådegran[7], Lennart Hansson[8], Einar Gude[1,2], Øystein Bjørtuft[9], Kjell Jansson[10], Hans Henrik Schultz[11], Dag Solbu[12] & Martin Iversen[11]

The NOCTET study randomized 282 patients ≥1 year after heart or lung transplantation to continue conventional calcineurin inhibitor (CNI) therapy or to start everolimus with reduced-exposure CNI. Last follow-up, at

vs. 6.4%). In conclusion, introducing everolimus in maintenance heart transplant patients, with reduced CNI, achieves a significant improvement in renal function which is maintained for at least 5 years, but an early renal benefit in lung transplant patients was lost. Long-term immunosuppressive efficacy was maintained.

BJCP British Journal of Clinical Pharmacology

Br J Clin Pharmacol / 78:1 / 24–32

Aber :

Impact of the reduction of calcineurin inhibitors on renal function in heart transplant patients: a systematic review and meta-analysis

Catherine Cornu,[1,2,3,4] Christophe Dufays,[1,2,3,4] Ségolène Gaillard,[1,2,3,4] François Gueyffier,[1,2,3,4] Michel Redonnet,[5] Laurent Sebbag,[6] Ana Roussoulières,[6] Christian A. Gleissner,[7] Jan Groetzner,[8] Hans B. Lehmkuhl,[9] Luciano Potena,[10] Lars Gullestad,[11,12] Marcelo Cantarovich[13] & Pascale Boissonnat[6]

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Calcineurin inhibitors (CNIs) lead to excellent short-term outcomes in heart transplant patients.
- Long-term use of CNIs may cause kidney damage.

WHAT THIS STUDY ADDS

- The risk/benefit ratio of CNI reduction after heart transplantation has not been demonstrated.
- There is a possible benefit on kidney function without raising the risk of acute rejection.

METHODS

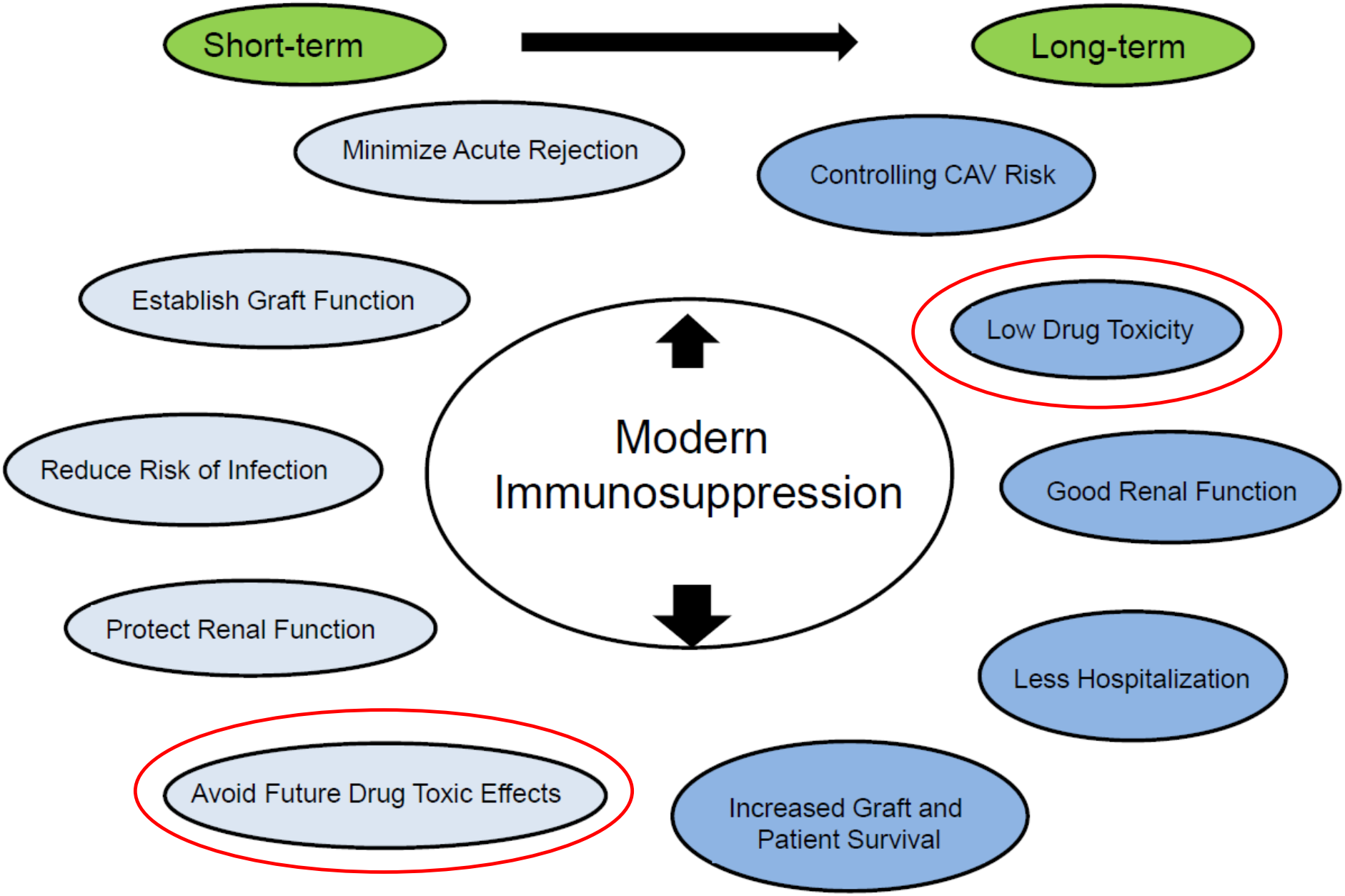
We carried out a systematic review and meta-analysis of randomized controlled trials on CNI reduction in heart transplant recipients. Primary outcomes were kidney function and acute rejection after 1 year. Secondary outcomes included graft loss, all-cause mortality and adverse events.

RESULTS

Eight open-label studies were included, with 723 patients (four tested *de novo* CNI reduction and four maintenance CNI reduction). Calcineurin inhibitor reduction did not improve creatinine clearance at 12

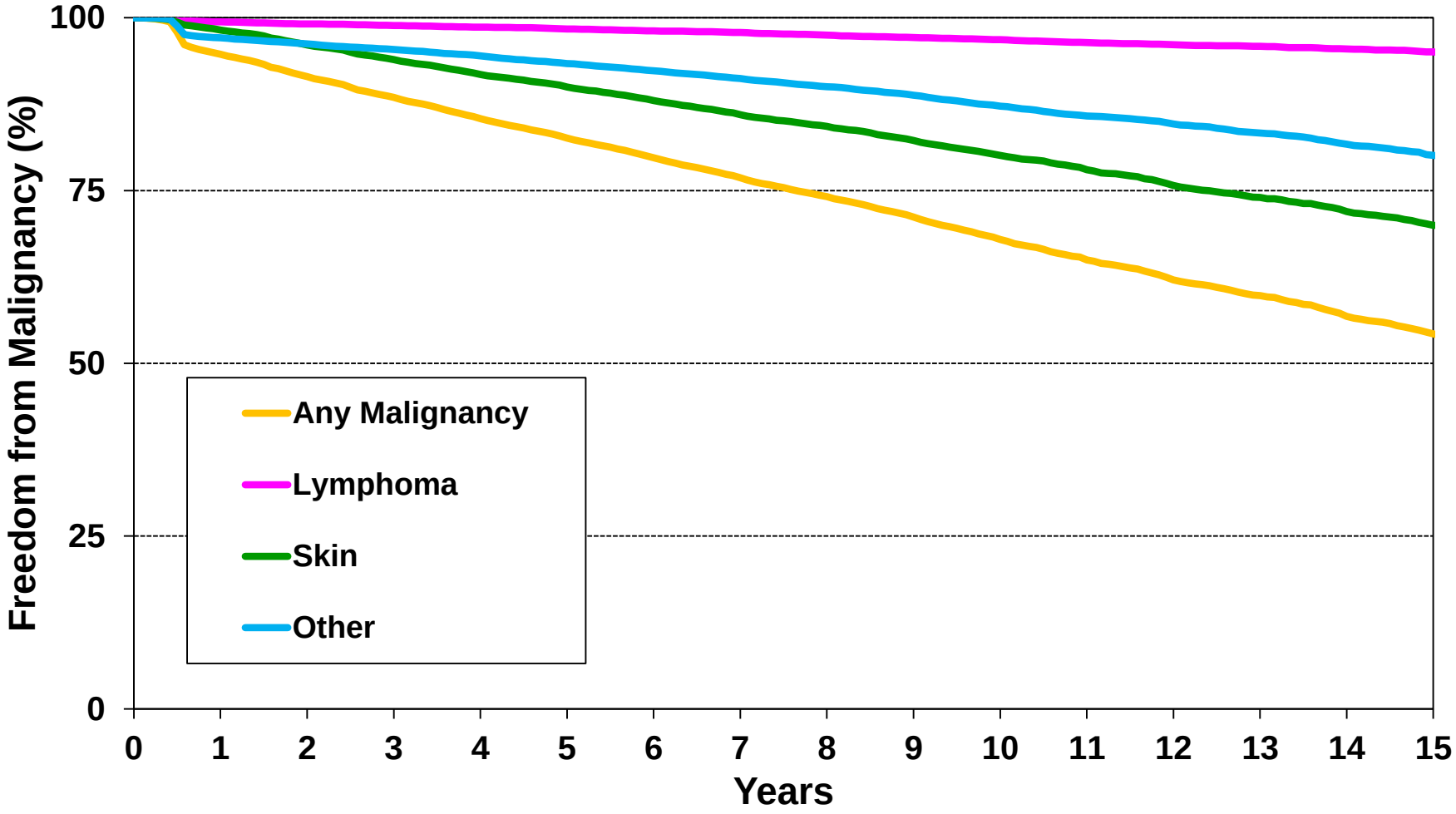
CONCLUSIONS

This meta-analysis did not demonstrate a favourable effect of CNI reduction on kidney function, but there was no increase in acute rejection. To provide a better analysis of the influence of CNI reduction patterns and associated treatments, a meta-analysis of individual patient data should be performed.



Barten MJ and Dieterlen MT Immunotherapy 2014

Adult Heart Transplants
Freedom from Malignancy by Type
(Transplants: January 1994 - June 2016)



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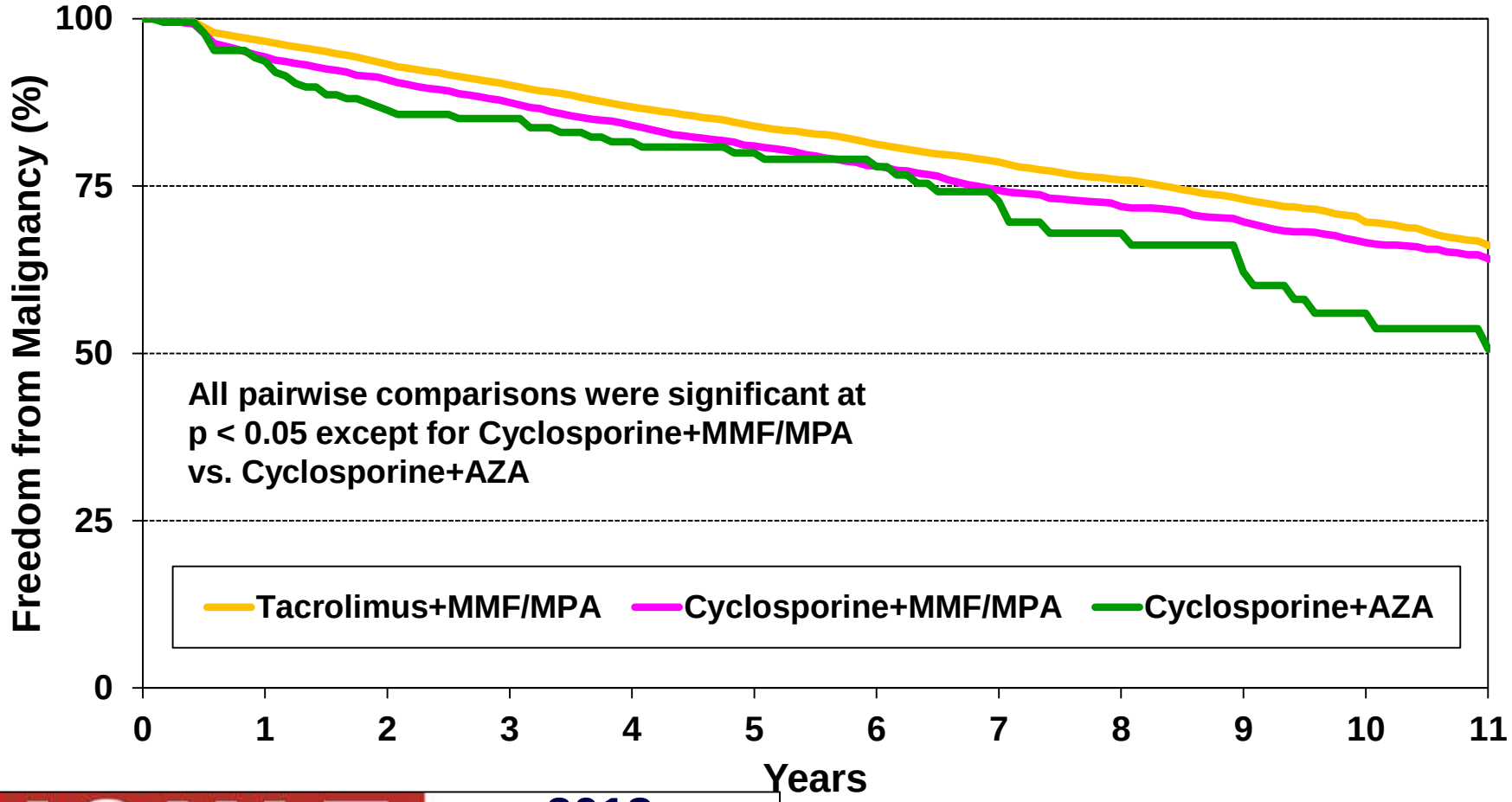
2018
JHLT. 2018 Oct; 37(10): 1155-1206

Skin malignancy includes melanoma and non-melanoma skin cancers.

Adult Heart Transplants
Freedom from Malignancy by Maintenance Immunosuppression Combinations at Discharge
Conditional on Survival to 14 days (Transplants: January 2004 – June 2016)



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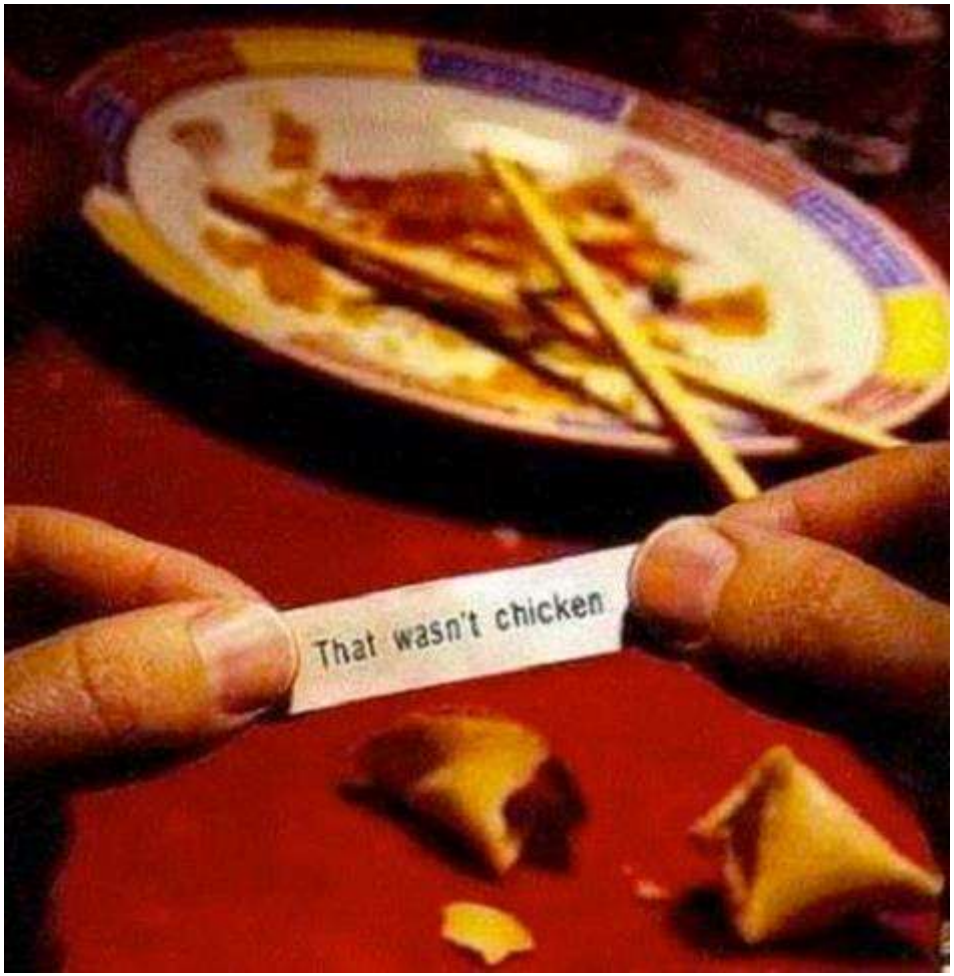
Zusammenfassung

- In den letzten Jahrzehnten gab es sowohl quantitativ als auch qualitativ eine immense Entwicklung im Bereich der Immunsuppression nach HTX.
- Die derzeit am häufigsten eingesetzte „Triple“-Therapie nach HTX besteht aus Tacrolimus, MMF und Steroiden.
- Die Abstossungshäufigkeit konnte in den letzten Jahren signifikant gesenkt werden.
- Durch Einsatz einer jeweils individualisierten Medikation ist eine signifikante Reduktion der Nebenwirkungen der Immunsuppressiva möglich.
- Eine weitere Verbesserung sollte in Zukunft möglich sein durch Verwendung pharmakogenomischer Analysen, Immunmonitoring, nicht-invasiver Abstossungsdiagnostik und gezielter Prophylaxe opportunistischer Infektionen.

Trotz sorgfältiger Individualisierung und Wahl der optimalen Therapiekonzepte für herztransplantierte Patienten ist bezüglich der Immunsuppression immer höchste Aufmerksamkeit erforderlich !!



Vielen Dank für Ihre Aufmerksamkeit

Herz- und Gefäßzentrum