UNIVERSITÄTS
KLINIKUM
HEIDELBERG

Collaborative Transplant Study
Rückblick und Ausblick

Gerhard Opelz
Institut für Immunologie

CTS

UK HD

CTS - Collaborative Transplant Study

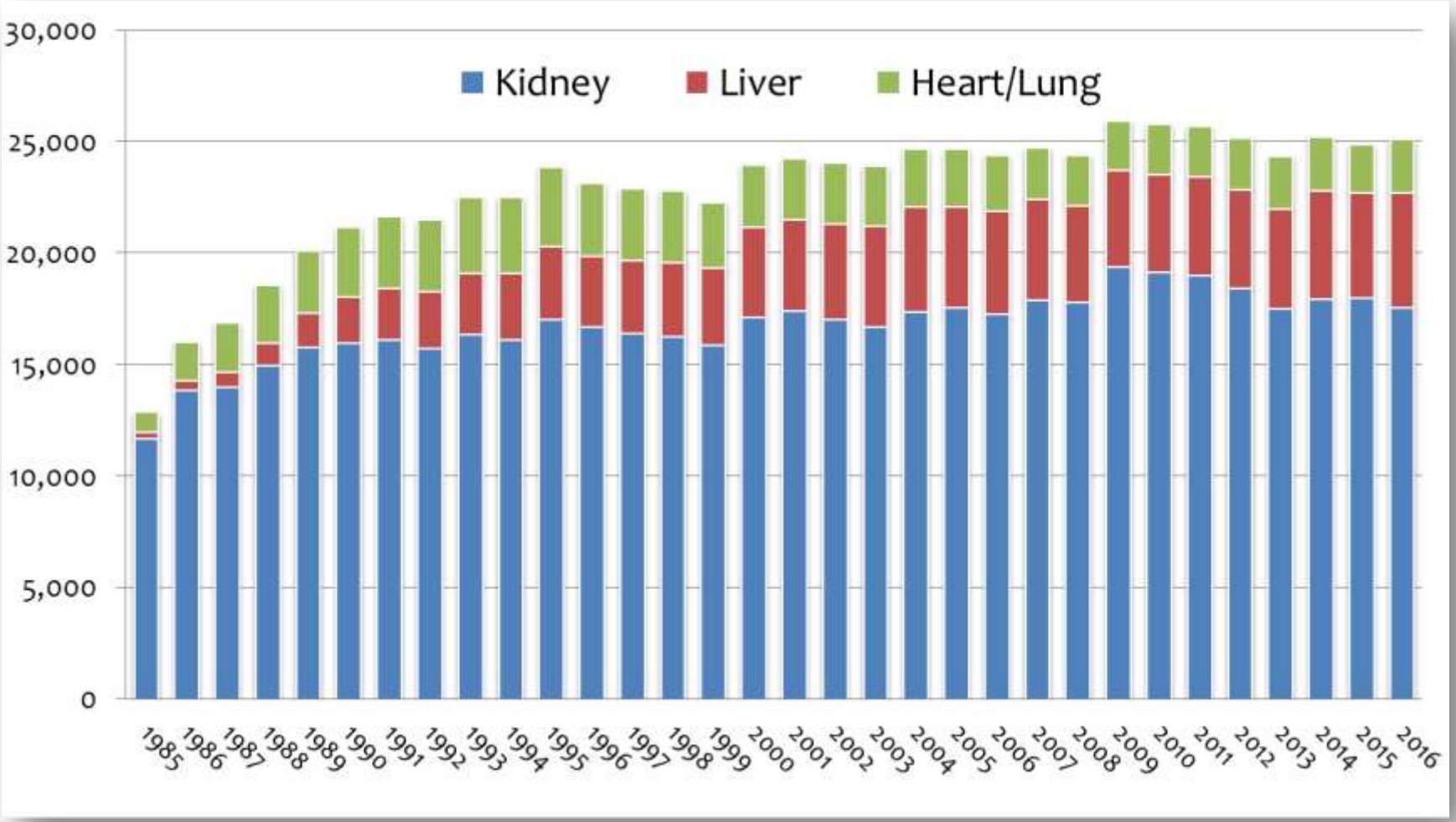
Initiated 1982

- Kidney / Pancreas
- Heart / Lung
- Liver

Priciples

- Scientific
- Voluntary
- Open to Everyone

Yearly Registered Transplants



Transpl Rev 27:43-45, 2013 (updated)

BJC British Journal of Cancer

British Journal of Cancer (2014) 110, 551–555 | doi: 10.1038/bjc.2013.725

Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence

C M Booth*,[1] and I F Tannock[2]

[1]Division of Cancer Care and Epidemiology, Queen's University Cancer Research Institute, 10 Stuart Street, Kingston, ON K7L 5PG, Canada and [2]Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada

Recent reports have highlighted the distinct roles and occasional tension between randomised controlled trials (RCTs) and population-based observational research (Concato, 2012; Hershman and Wright, 2012; Goodwin *et al*, 2013). In this commentary, we will discuss the relative strengths and limitations of each form of research (see Table 1), and propose that well-designed RCTs and population-based observational studies can serve as complementary forms of research to ensure that the results of clinical trials translate into tangible benefits in the general population.

<10% of patients with cancer are entered onto a clinical trial. Patients with advanced age and greater comorbidity (Hutchins *et al*, 1999; Lewis *et al*, 2003), and those from lower socioeconomic background (Unger *et al*, 2013) are under-represented in RCTs. There can also be important differences in the provision of care for patients on RCTs (i.e., highly regulated trial protocols at specialised centres of excellence) compared with patients in routine practice. Given the greater toxicity that is expected when a treatment is applied to a non-selected population with greater comorbidity than

Advantages of Observational Studies

- reflects clinical routine
- includes patients at high risk
- rare diseases
- large patient numbers
- long observation time
- allows study of secondary effects

1991

THE LANCET

Survival of DNA HLA-DR typed and matched cadaver kidney transplants

GERHARD OPELZ JOANNIS MYTILINEOS SABINE SCHERER
HEATHER DUNCKLEY JEAN TREJAUT JEREMY CHAPMAN
DEREK MIDDLETON DAVID SAVAGE OTTFRIED FISCHER
JEAN-DENIS BIGNON JEAN-CLAUDE BENSA EKKEHARD ALBERT
HARRIET NOREEN

FOR THE COLLABORATIVE TRANSPLANT STUDY

The clinical value of serological HLA matching for cadaver kidney transplantation remains uncertain because the success rate for HLA-matched cadaver transplants is lower than that of HLA-matched sibling grafts. Up to 25% of serological HLA-DR typings may be incorrect when compared with a more accurate DNA-RFLP method, and we have

Introduction

The clinical value of HLA matching for cadaver kidney transplantation remains uncertain.[1,2] Speculation continues about the existence of histocompatibility loci, other than the routinely used HLA A, B, and DR antigens, which may be important in renal transplantation. This possibility arises from the observation that the success rate of HLA-matched

Lancet 338: 461–463, 1991

DNA Typing

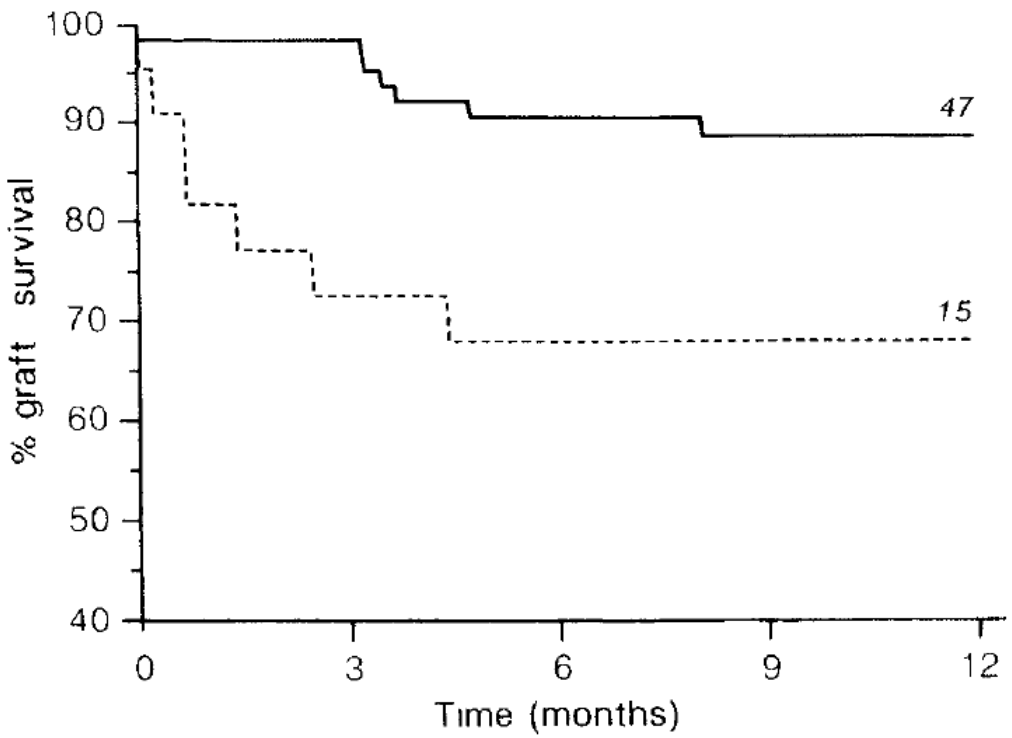


Fig 1—Survival rates of DNA HLA A, B, DR matched first cadaver kidney grafts.

———, No DNA HLA-DR mismatch (n = 64); – – –, DNA HLA-DR mismatch present (n = 22). Figures shown refer to the final number of patients with functioning grafts at one year.

Lancet 338: 461–463, 1991

2004

American Journal of Transplantation

ASTS

OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF TRANSPLANTATION AND THE AMERICAN SOCIETY OF TRANSPLANT SURGEONS

UNOS

UNITED NETWORK FOR ORGAN SHARING

American Journal of Transplantation 2004; 4: 1501–1508
Blackwell Munksgaard

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doi: 10.1111/j.1600-6143.2004.00535.x

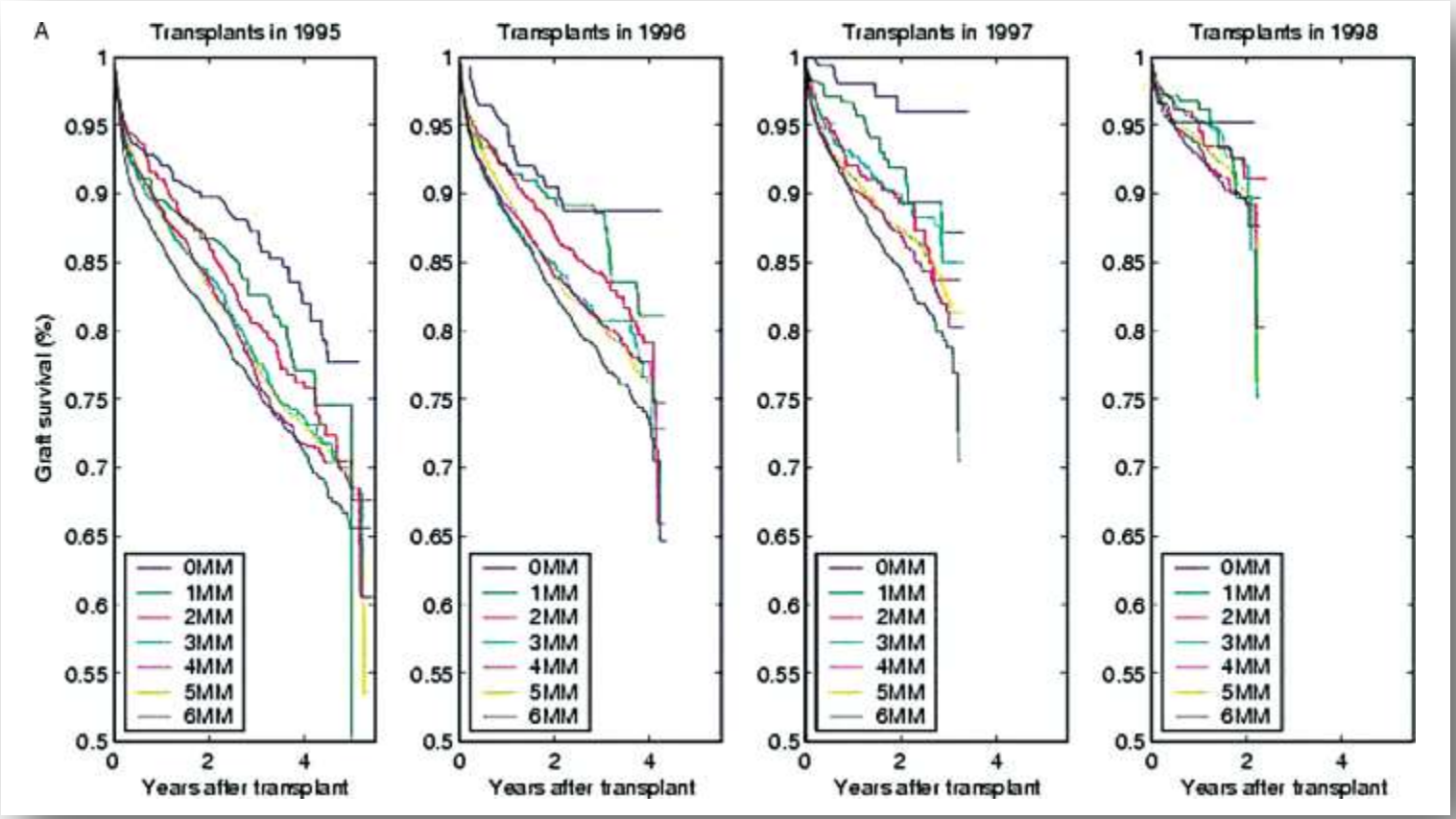
Diminishing Significance of HLA Matching in Kidney Transplantation

Xuanming Su[a], Stefanos A. Zenios[a], Harini Chakkera[b], Edgar L. Milford[c] and Glenn M. Chertow[b,*]

The pace of ESRD program growth has been attenuated owing to a distressingly high mortality rate among individuals on dialysis (>20% annually). Survival appears to be significantly enhanced with kidney transplantation, although

UK HD

HLA Mismatches



„With evolving clinical practice, including the provision of safer and more potent immunosuppressive therapy, the significance of HLA matching has diminished.“

Am J Transplant 4: 1501–1508, 2004

2007

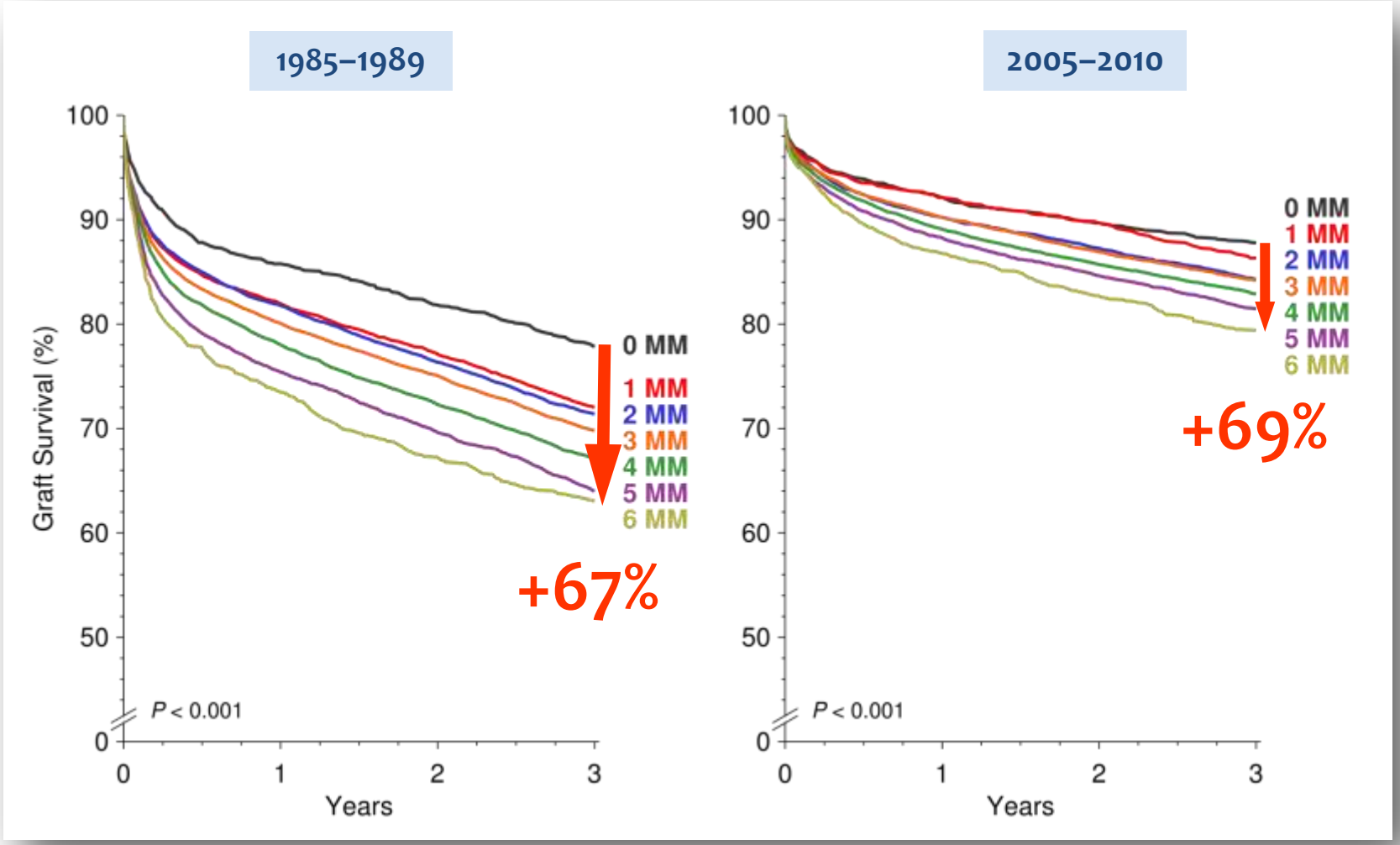
LIPPINCOTT WILLIAMS & WILKINS
Transplantation
THE OFFICIAL JOURNAL OF THE TRANSPLANTATION SOCIETY

SPECIAL FEATURE

Effect of Human Leukocyte Antigen Compatibility on Kidney Graft Survival: Comparative Analysis of Two Decades

Gerhard Opelz and Bernd Döhler

HLA-A+B+DR Mismatches



2016

LIPPINCOTT WILLIAMS & WILKINS
Transplantation
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Original Clinical Science—General

OPEN

The Risk of Transplant Failure With HLA Mismatch in First Adult Kidney Allografts From Deceased Donors

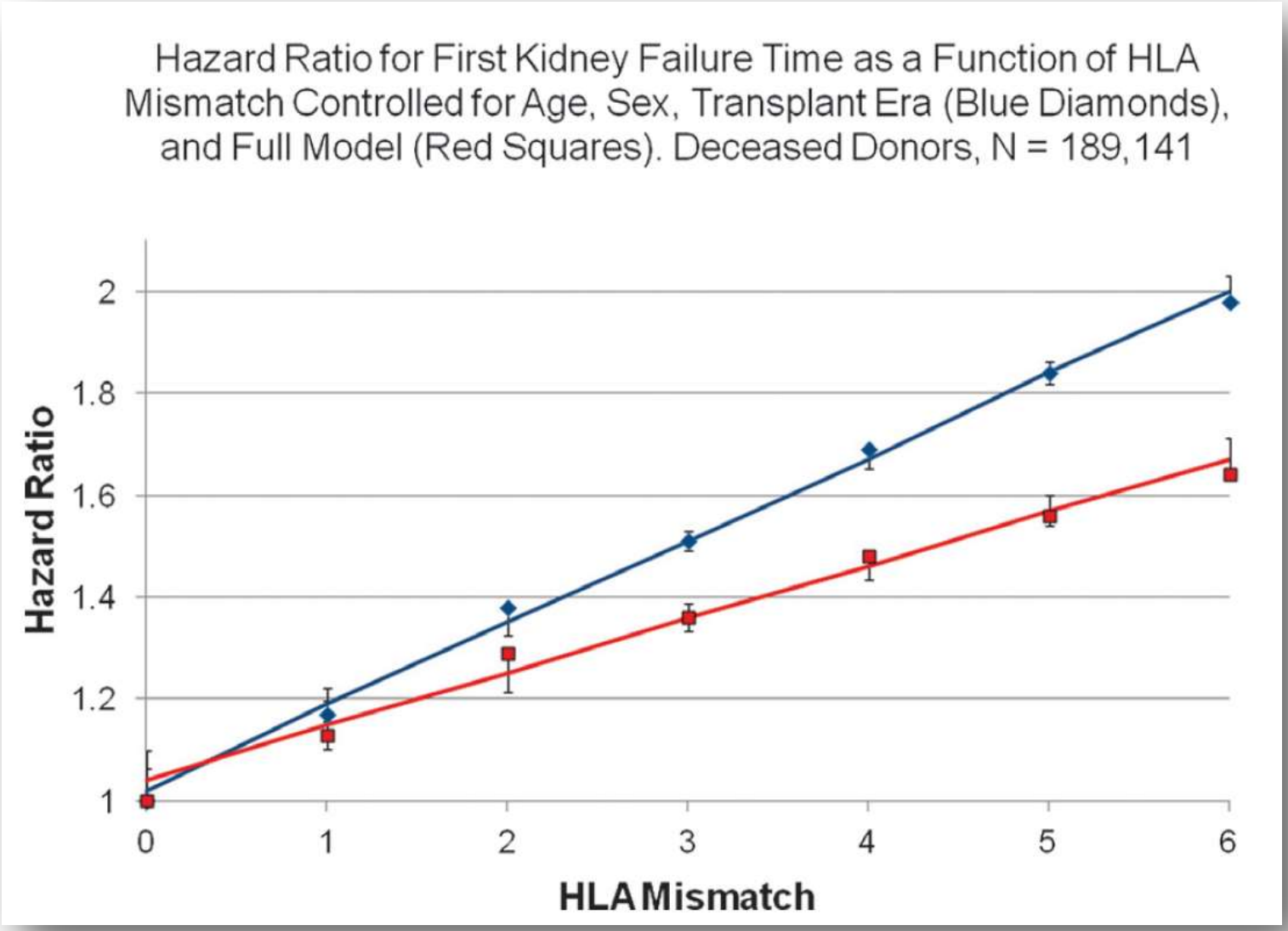
Robert C. Williams, PhD,[1] Gerhard Opelz, MD,[2] Chelsea J. McGarvey, MD,[3] E. Jennifer Weil, MD,[1] and Harini A. Chakkera, MD[4]

Background. Since the beginning of the technology, there has been active debate about the role of human leucocyte antigen (HLA) matching in kidney allograft survival. Recent studies have reported diminishing importance of HLA matching, which have, in turn, been challenged by reports that suggest the continuing importance of these loci. Given the controversies, we examined the effect of HLA compatibility on kidney allograft survival by studying all first adult kidney transplants in the United States from a deceased donor. **Methods.** Using the United Network for Organ Sharing data, we identified first deceased donor kidney transplants between October 1, 1987, and December 31, 2013. Recipients were classified by their number of HLA mismatches. Cox multivariate regression analyses adjusting for recipient and donor transplant characteristics were performed to determine the impact of HLA compatibility on kidney allograft survival. **Results.** Study cohort included 189 141 first adult kidney alone transplants, with a total of 994 558 years of kidney allograft follow-up time. Analyses adjusted for recipient and donor characteristics demonstrated a 13% higher risk (hazard ratio, 1.13; 95% confidence interval, 1.06-1.21) with 1 mismatch and a 64% higher risk (hazard ratio, 1.64, 95% confidence interval, 1.56-1.73) with 6 mismatches. Dividing the mismatch categories into 27 ordered permutations, and testing their 57 within mismatch category differences, demonstrated that all but 1 were equal, independent of locus. **Conclusions.** A significant linear relationship of hazard ratios was associated with HLA mismatch and affects allograft survival even during the recent periods of increasing success in renal transplantation.

(*Transplantation* 2016;100: 1094–1102)

UK HD

HLA-A+B+DR Mismatches



Transplantation 100: 1094–1102, 2016

2005

THE LANCET

Mechanisms of Disease

Non-HLA transplantation immunity revealed by lymphocytotoxic antibodies

Lancet 2005; 365: 1570–76

See Comment page 1522

*Centres listed at the end of the paper

Department of Transplantation Immunology, Institute of Immunology, University of Heidelberg, Im Neuenheimer Feld 305, D-69120 Heidelberg, Germany (Prof G Opelz MD)

Correspondence to: Prof Gerhard Opelz gerhard.opelz@med.uni-heidelberg.de

*Gerhard Opelz for the Collaborative Transplant Study**

Summary

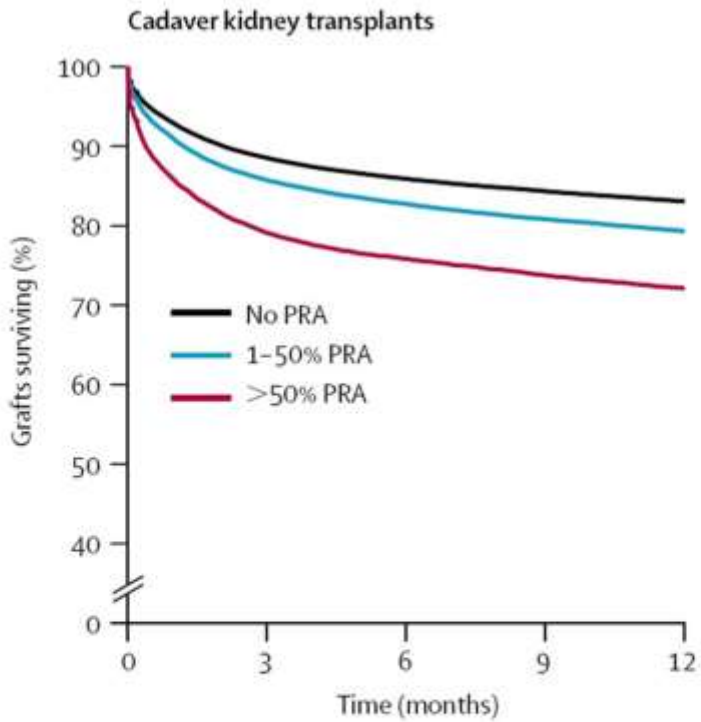
Background The presence of panel-reactive antibodies (PRA) against HLA antigens before transplantation is associated with early rejection of kidney grafts from cadaver donors. Transplants from HLA-identical sibling donors do not provide a target for antibodies to HLA antigens and should therefore not be affected by PRA.

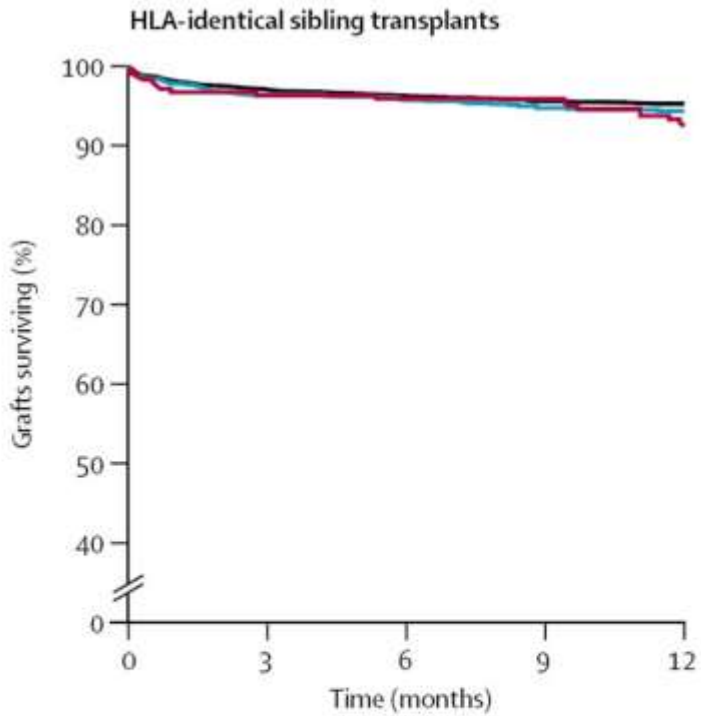
Methods Data from the Collaborative Transplant Study were used to examine the influence of PRA on graft survival. Uncensored graft survival and death-censored graft survival were calculated, and the data were analysed by multivariate Cox's regression methods.

Findings Among recipients of HLA-identical sibling transplants, 3001 patients with no PRA had significantly higher 10-year graft survival (72·4% [SE 1·1]) than 803 patients with 1–50% PRA (63·3% [2·5]; p=0·0006) or 244 patients

Pretransplant PRA

Kidney Transplants





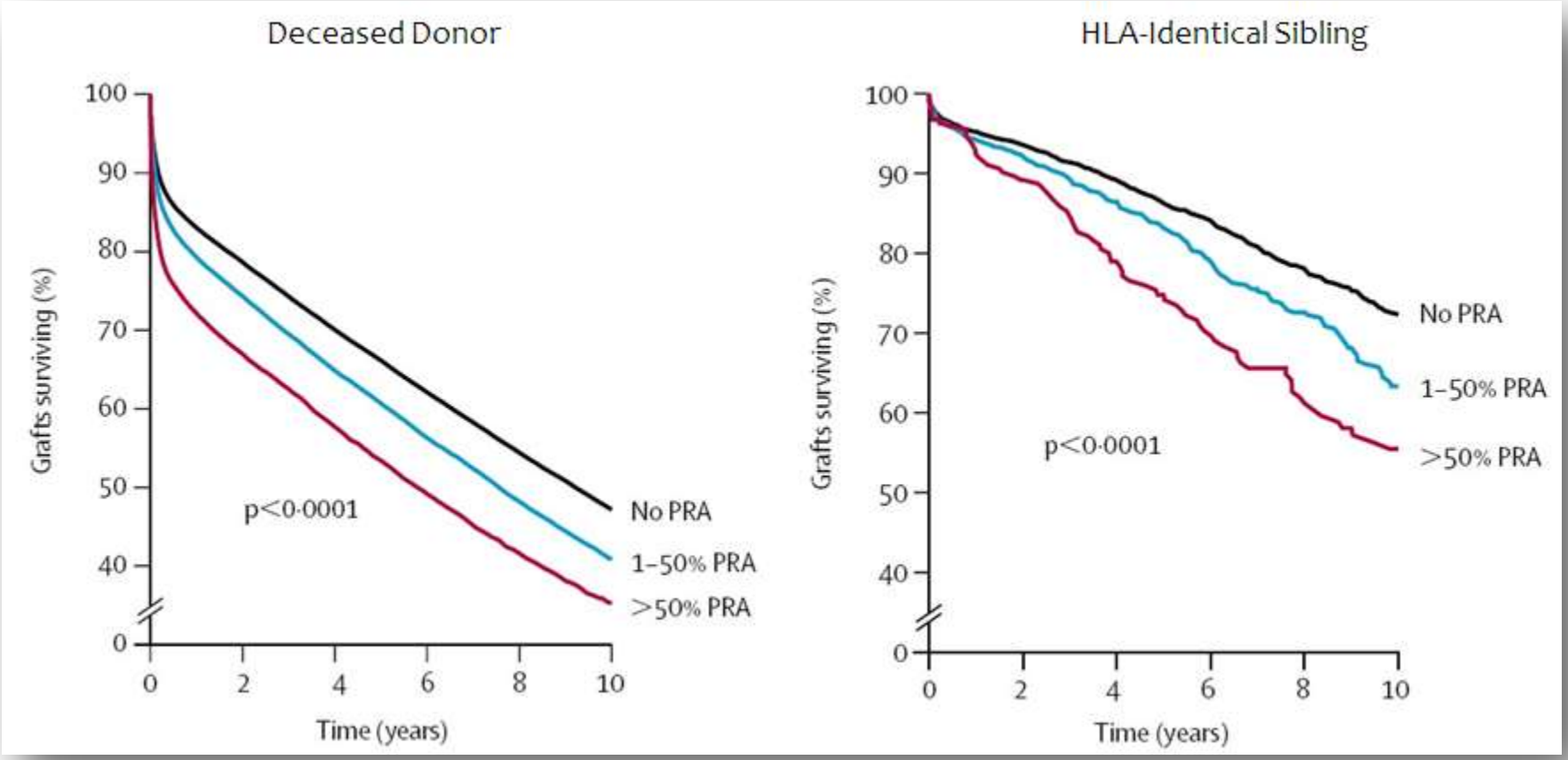
Number of transplants					
No PRA	116562	103234	99382	95688	94252
1–50% PRA	36314	31155	29889	28827	28288
>50% PRA	7610	6019	5724	5473	5349

Number of transplants					
No PRA	3001	2914	2864	2774	2765
1–50% PRA	803	774	766	744	741
>50% PRA	244	235	229	223	215

Lancet 365: 1570–1576, 2005

Pretransplant PRA

Kidney Transplants



Lancet 365: 1570–1576, 2005

2008

American Journal of Transplantation
AST
ASTS
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American Journal of Transplantation 2008; 8: 95–102
Blackwell Munksgaard

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doi: 10.1111/j.1600-6143.2007.02042.x

Role of Minor Histocompatibility Antigens in Renal Transplantation

A. Heinold, G. Opelz, S. Scherer, A. Ruhenstroth, G. Laux, B. Doehler and T. H. Tran*

Department of Transplantation Immunology, Institute of Immunology, University of Heidelberg, Heidelberg, Germany
**Corresponding author: T. Hien Tran, hien.tran@med.uni-heidelberg.de*

duced that 38% of graft failures are due to non-HLA factors, 18% to HLA factors and 43% to nonimmunologic factors (2).

It can be reasonably hypothesized that an alloimmune response evoked by minor histocompatibility antigens (mHags) might lead to graft rejection. The mHags are polymorphic cell-derived self-peptides, encoded by sex-linked

UK HD

2007

The NEW ENGLAND JOURNAL of MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

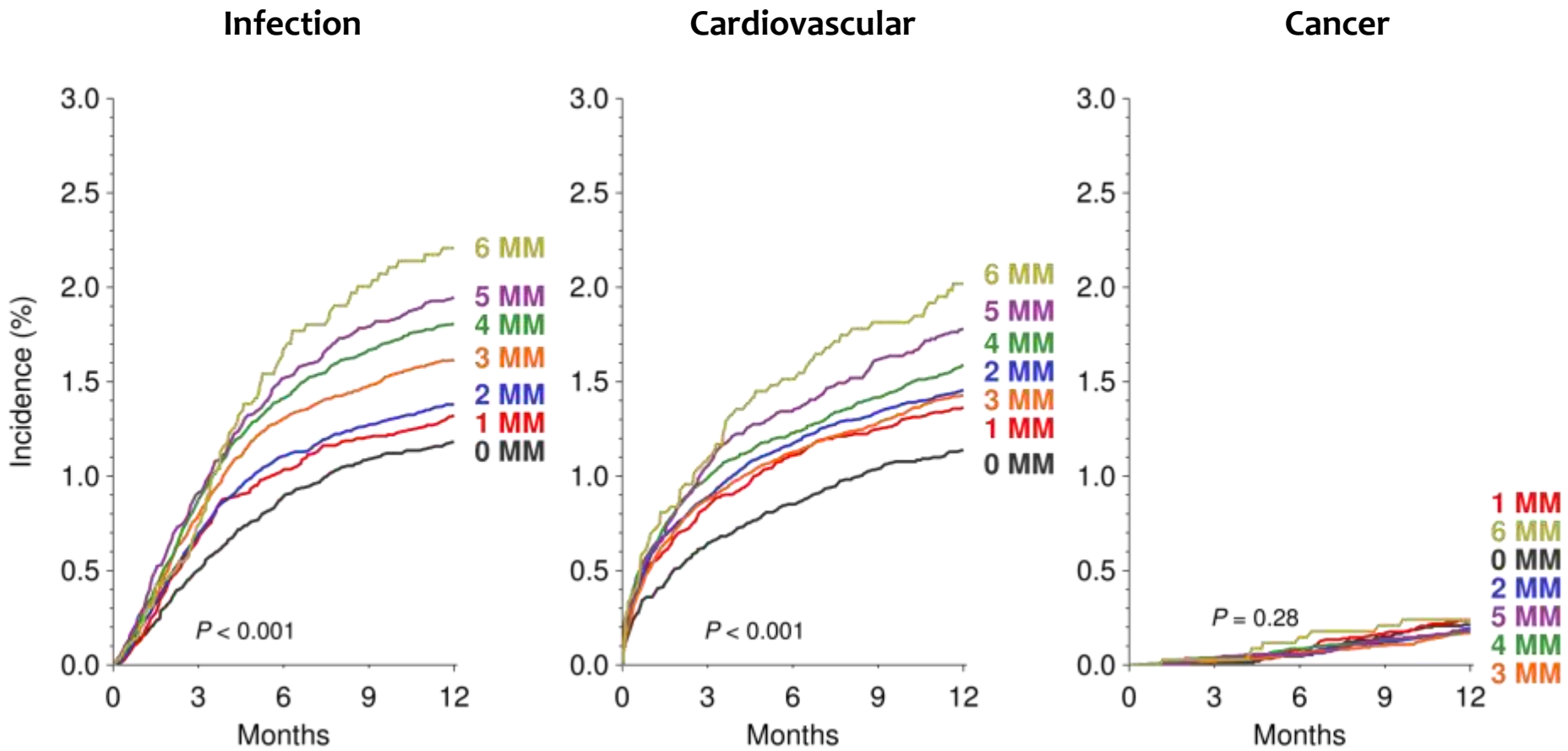
Antibodies against MICA Antigens and Kidney-Transplant Rejection

Yizhou Zou, M.D., Peter Stastny, M.D., Caner Süsal, M.D., Bernd Döhler, Ph.D., and Gerhard Opelz, M.D.

New Engl J Med 357: 1293–1300, 2007

American Journal of Transplantation
AST
ASTS
OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF TRANSPLANTATION AND THE AMERICAN SOCIETY OF TRANSPLANT SURGEONS

Death with functioning graft because of ...
(N = 177,584)



Am J Transplant 12: 3031–3038, 2012

Most Cited

THE LANCET

THE LANCET

Incidence of non-Hodgkin lymphoma in kidney and heart transplant recipients

Gerhard Opelz, Robin Henderson, for the Collaborative Transplant Study

Lancet 1993; **342:** 1514–16

American Journal of Transplantation

American Journal of Transplantation 2003; 4: 222–230
Blackwell Munksgaard

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doi: 10.1046/j.1600-6143.2003.00325.x

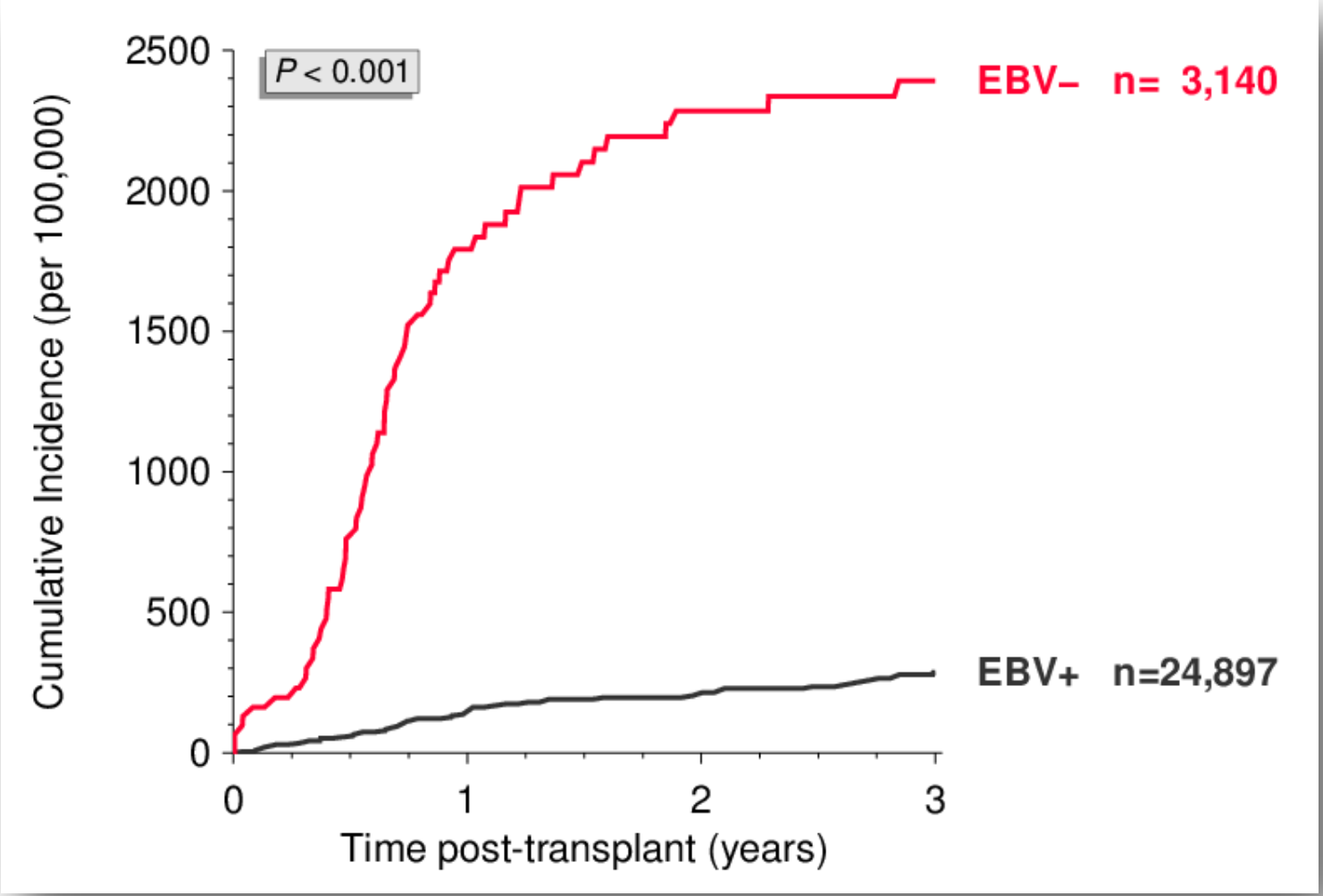
Lymphomas After Solid Organ Transplantation: A Collaborative Transplant Study Report

Gerhard Opelz* and Bernd Döhler

tranodal involvement, a more aggressive clinical course, poorer response to conventional therapies, and poorer out-

Non-Hodgkin Lymphoma – EBV Status

Kidney Transplants 1995–2012



Transplantation 88: 962–967, 2009

Most Cited

THE LANCET

THE LANCET

Incidence of non-Hodgkin lymphoma in kidney and heart transplant recipients

Gerhard Opelz, Robin Henderson, for the Collaborative Transplant Study

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doi: 10.1046/j.1600-6143.2003.00325.x

Lymphomas After Solid Organ Transplantation: A Collaborative Transplant Study Report

Gerhard Opelz* and Bernd Döhler

tranodal involvement, a more aggressive clinical course, poorer response to conventional therapies, and poorer out-

kidney INTERNATIONAL

Association of chronic kidney graft failure with recipient blood pressure

GERHARD OPELZ, THOMAS WUJCIAK and EBERHARD RITZ, for the COLLABORATIVE TRANSPLANT STUDY

Kidney International, Vol. 53 (1998), pp. 217–222

1998

kidney INTERNATIONAL ISN Official journal of the International Society of Nephrology

Kidney International, Vol. 53 (1998), pp. 217–222

Association of chronic kidney graft failure with recipient blood pressure

GERHARD OPELZ, THOMAS WUJCIAK and EBERHARD RITZ, for the COLLABORATIVE TRANSPLANT STUDY

Department of Transplantation Immunology and Department of Nephrology, University of Heidelberg, Heidelberg, Germany

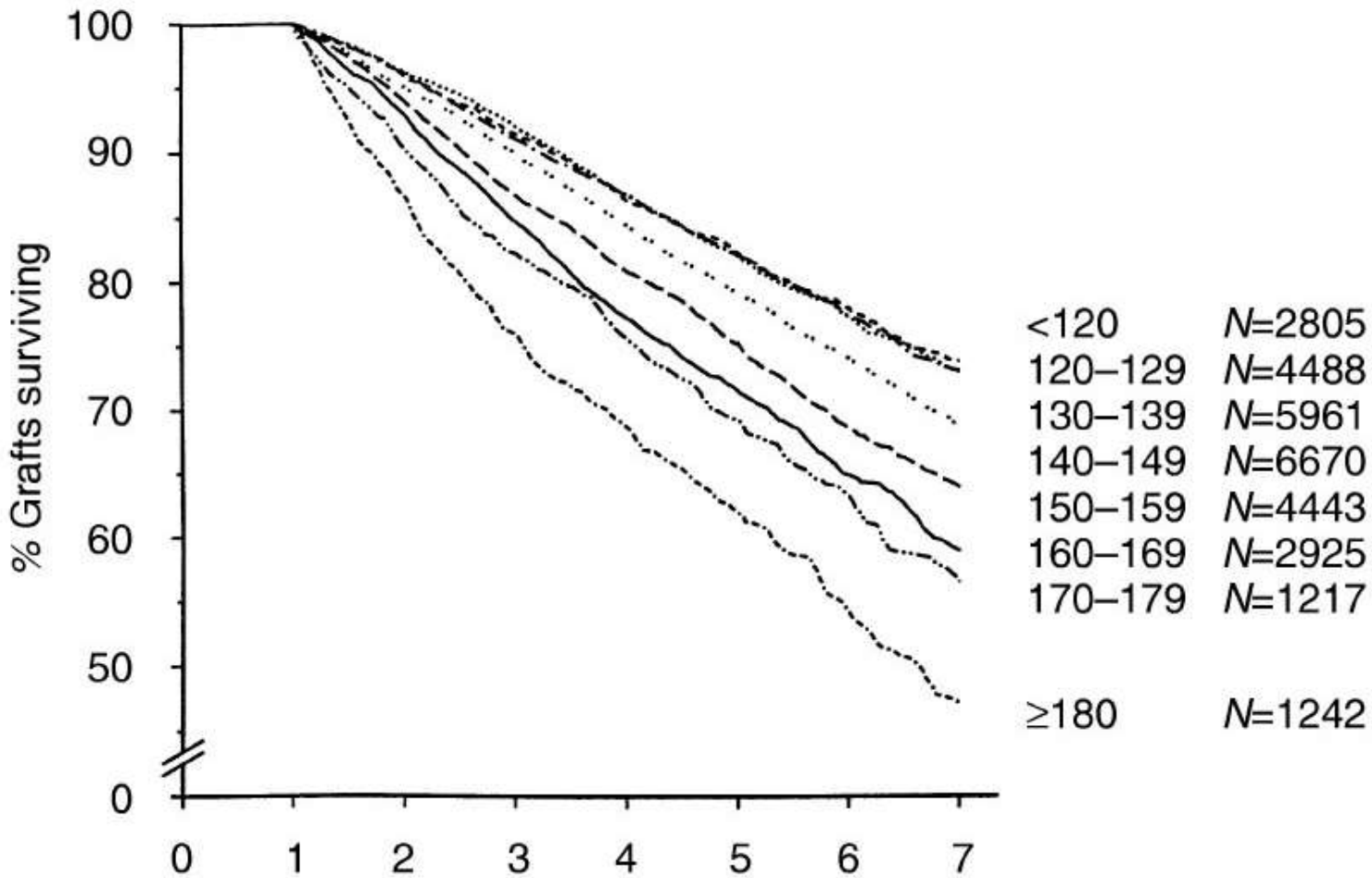
Association of chronic kidney graft failure with recipient blood pressure. Immunological rejection is the most important cause of kidney transplant failure. Recently, nonimmunological causes of long-term allograft failure have become more widely appreciated. In primary chronic renal disease, blood pressure is of overriding importance for long-term renal function. The role of blood pressure in determining long-term

means of antihypertensive medication reduces the rate of functional deterioration [12].

In 1988, with the aim of examining the relationship between blood pressure and long-term graft outcome in a large patient cohort, we started to include post-transplant blood pressure

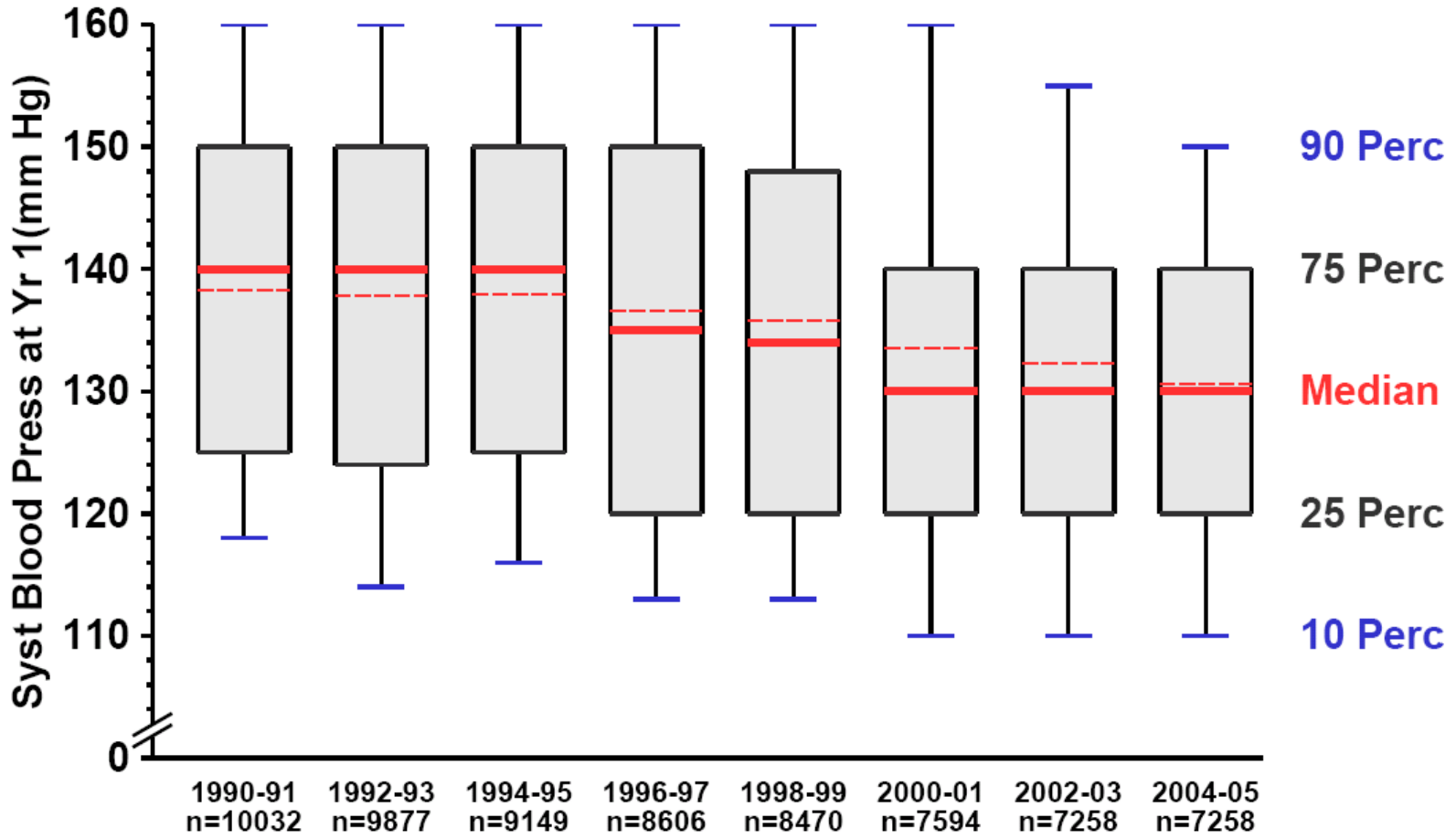
Systolic Blood Pressure

Kidney Transplants



Kidney Int 53: 217–222, 1998

1-Year Systolic Blood Pressure



2005

American Journal of Transplantation
ASTS
ASTS
OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF TRANSPLANTATION AND THE AMERICAN SOCIETY OF TRANSPLANT SURGEONS

American Journal of Transplantation 2005; 5: 2725–2731
Blackwell Munksgaard

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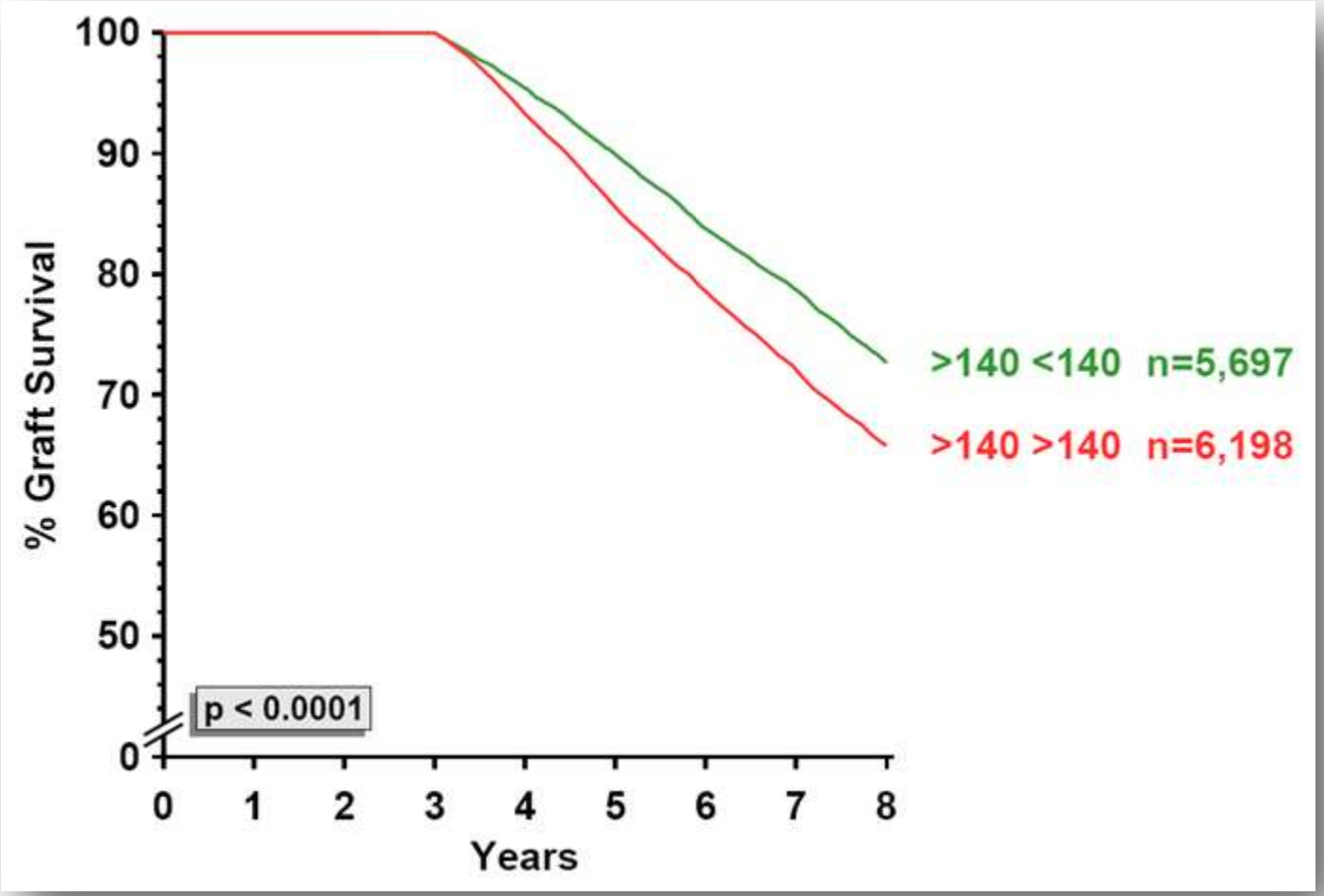
doi: 10.1111/j.1600-6143.2005.01093.x

Improved Long-Term Outcomes After Renal Transplantation Associated with Blood Pressure Control

Gerhard Opelz* and Bernd Döhler for the Collaborative Transplant Study

mediators of reduced long-term renal function. In the non-transplant setting, elevation of blood pressure (BP) plays a significant role in the production of progressive renal dam-

Systolic Blood Pressure at 1 und 3 Years



Am J Transplant 5: 2725–2731, 2005

2018

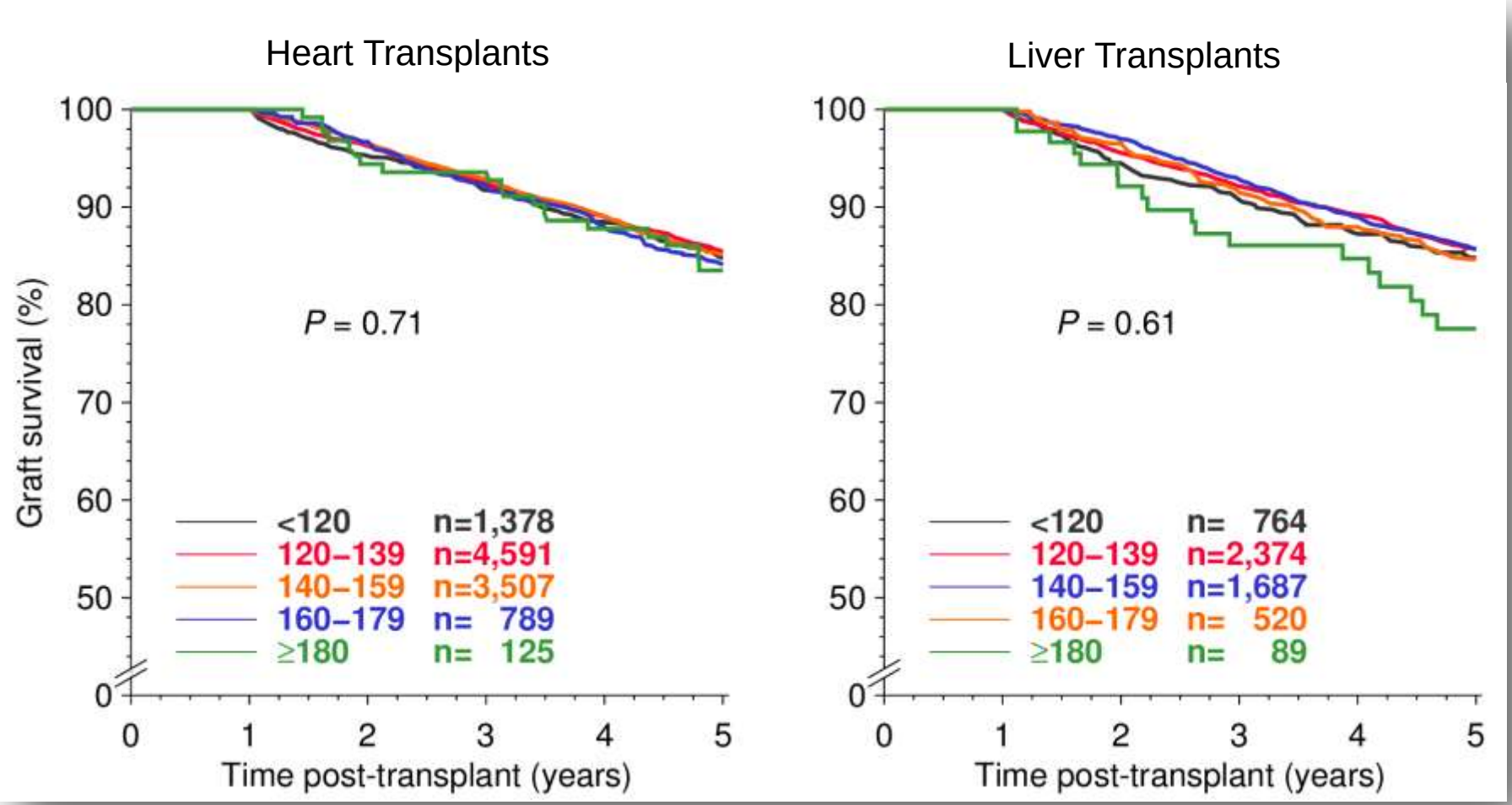
Lippincott Williams & Wilkins
Transplantation
THE OFFICIAL JOURNAL OF THE TRANSPLANTATION SOCIETY

Transplantation Publish Ahead of Print
DOI: 10.1097/TP.0000000000002023

Influence of Blood Pressure and Calcineurin Inhibitors on Kidney Function After Heart or Liver Transplantation

Christian Morath, MD,[1] Gerhard Opelz, MD,[2] Bernd Döhler, PhD,[2]
Martin Zeier, MD,[1] and Caner Süsal, MD[2]

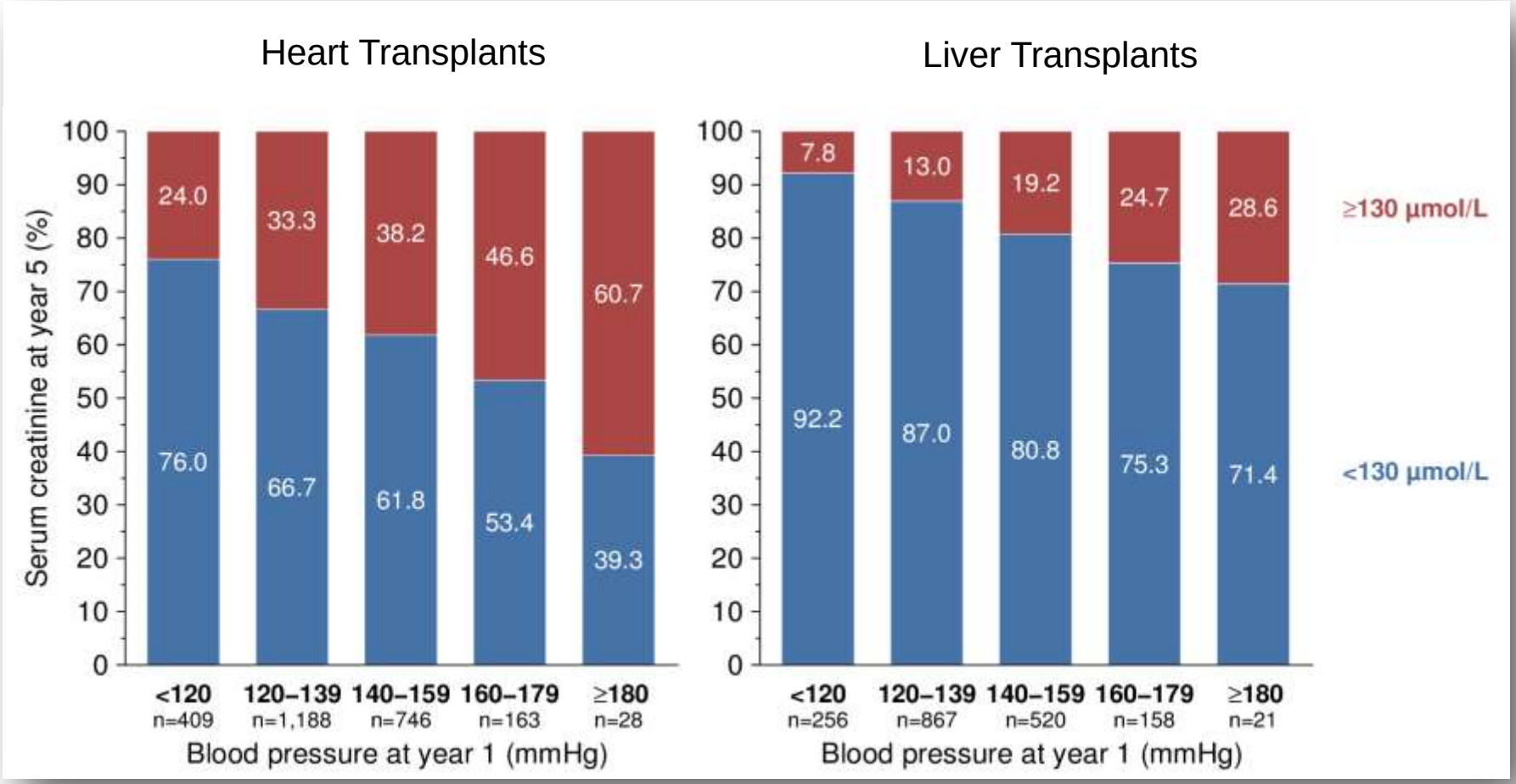
Systolic Blood Pressure



Transplantation, ahead of print, 2018

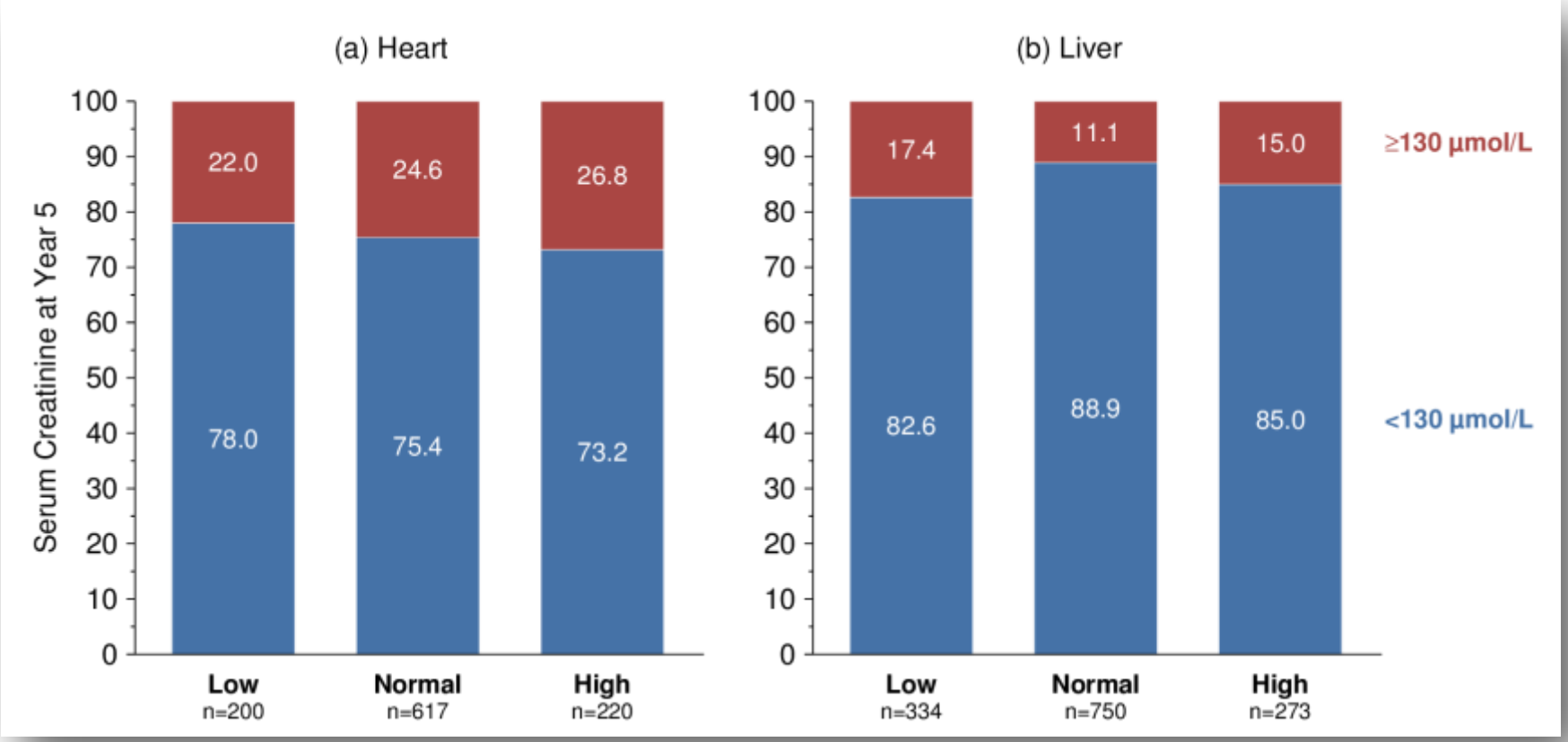
5-Year Serum Creatinine

1-year creatinine <130



CNI Dosage

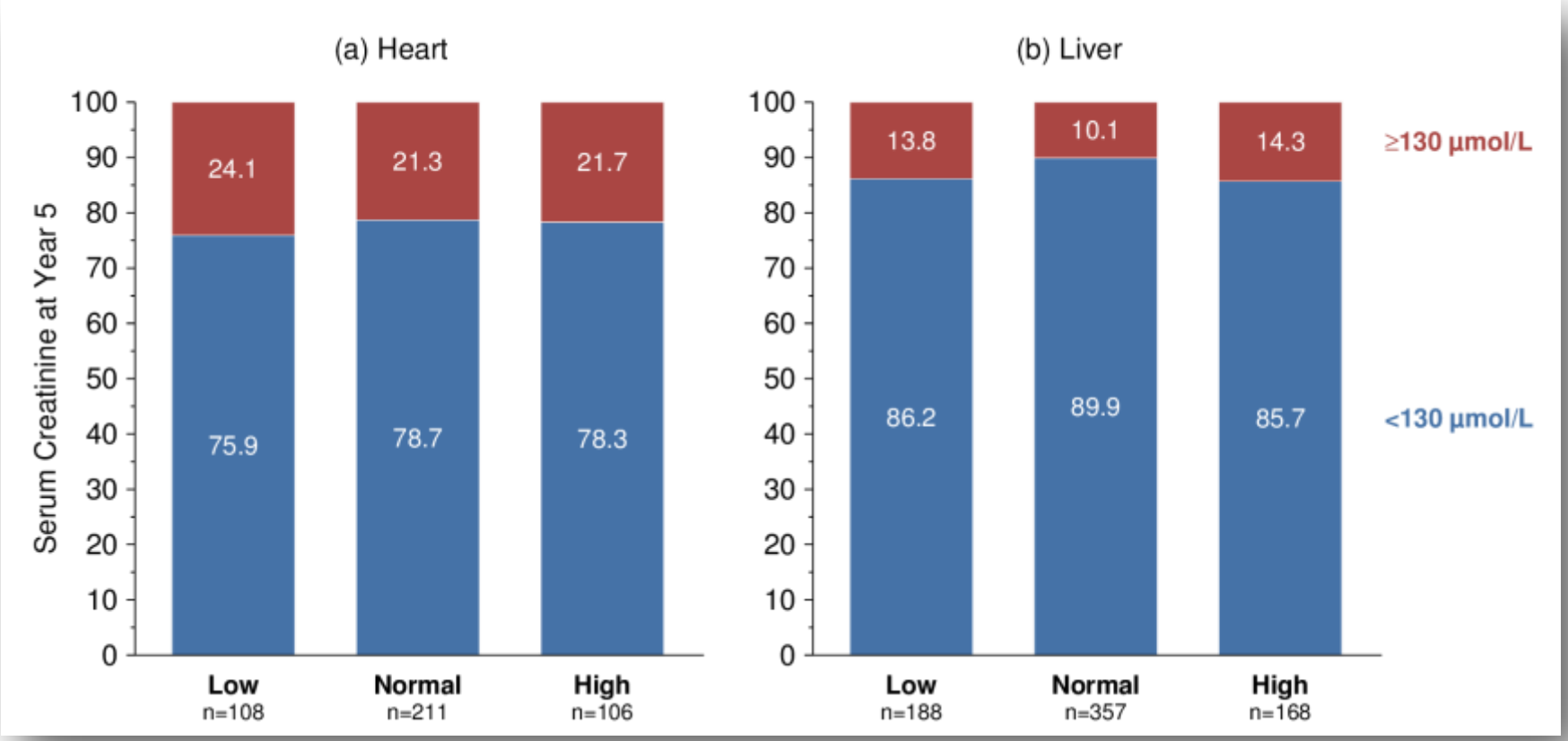
Transplants 1995–2014



Transplantation, ahead of print, 2018

CNI Trough Level

Transplants 1995–2014



2006

JASN® Journal of the American Society of Nephrology

Angiotensin-Converting Enzyme Inhibitor or Angiotensin II Type 1 Receptor Antagonist Therapy Is Associated with Prolonged Patient and Graft Survival after Renal Transplantation

Georg Heinze,* Christa Mitterbauer,† Heinz Regele,‡ Reinhard Kramar,§ Wolfgang C. Winkelmayer,‖ Gary C. Curhan,¶ and Rainer Oberbauer†

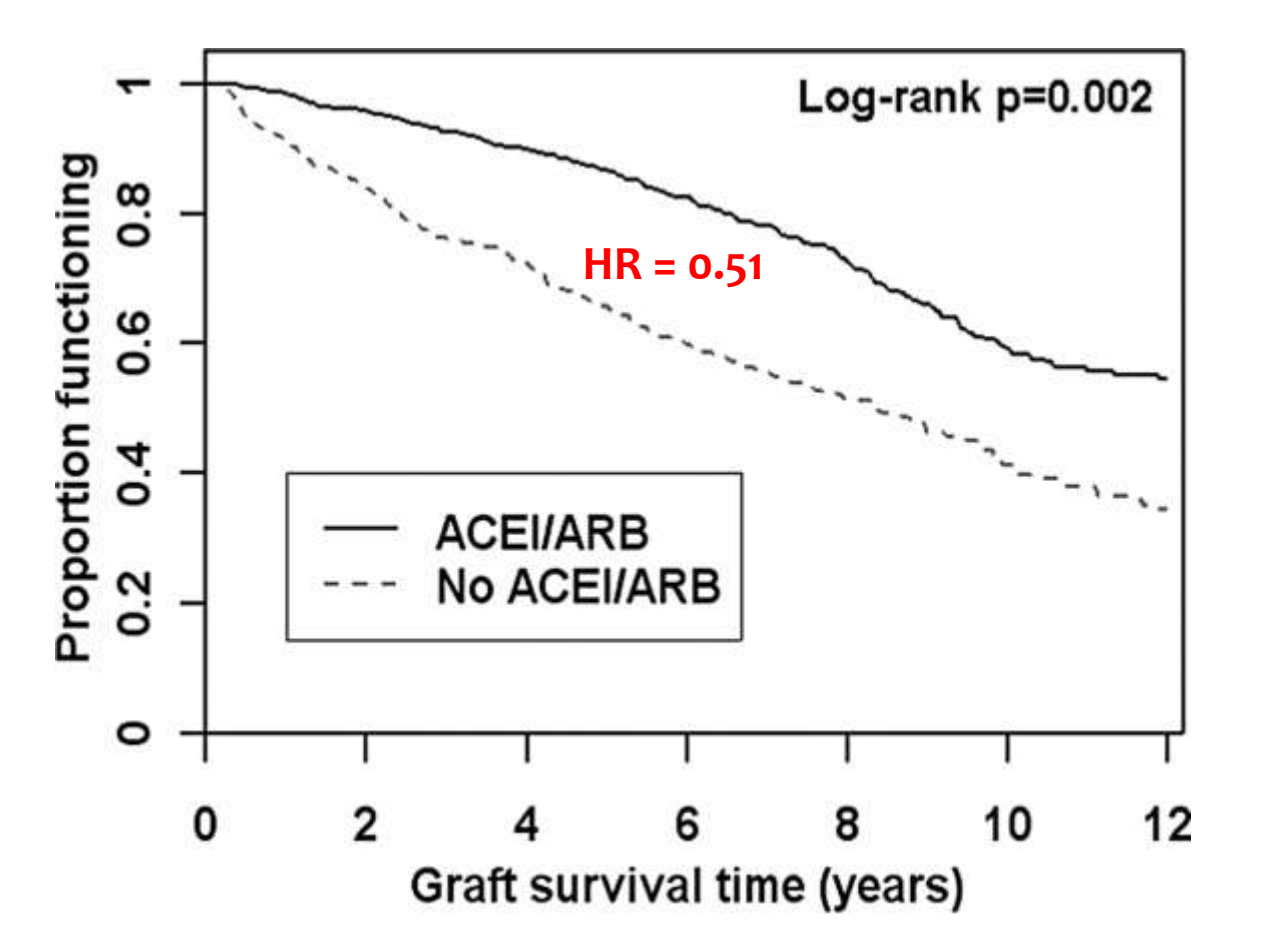
*Core Unit of Medical Statistics and Informatics, Departments of †Nephrology and ‡Pathology, Medical University of Vienna, Vienna, and §Austrian Dialysis and Transplant Registry, Hospital Wels, Wels, Austria; and ‖Division of Pharmacoepidemiology and Pharmacoeconomics and Renal Division, and ¶Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

J Am Soc Nephrol 17: 889–899, 2006

UK HD

ACEI / ARB

First Kidney Transplants 1990–2003 Vienna (n=2,031)



J Am Soc Nephrol 17: 889–899, 2006

UK HD

JASN® Journal of the American Society of Nephrology

No Improvement of Patient or Graft Survival in Transplant Recipients Treated with Angiotensin-Converting Enzyme Inhibitors or Angiotensin II Type 1 Receptor Blockers: A Collaborative Transplant Study Report

Gerhard Opelz,* Martin Zeier,† Gunter Laux,* Christian Morath,† and Bernd Döhler*

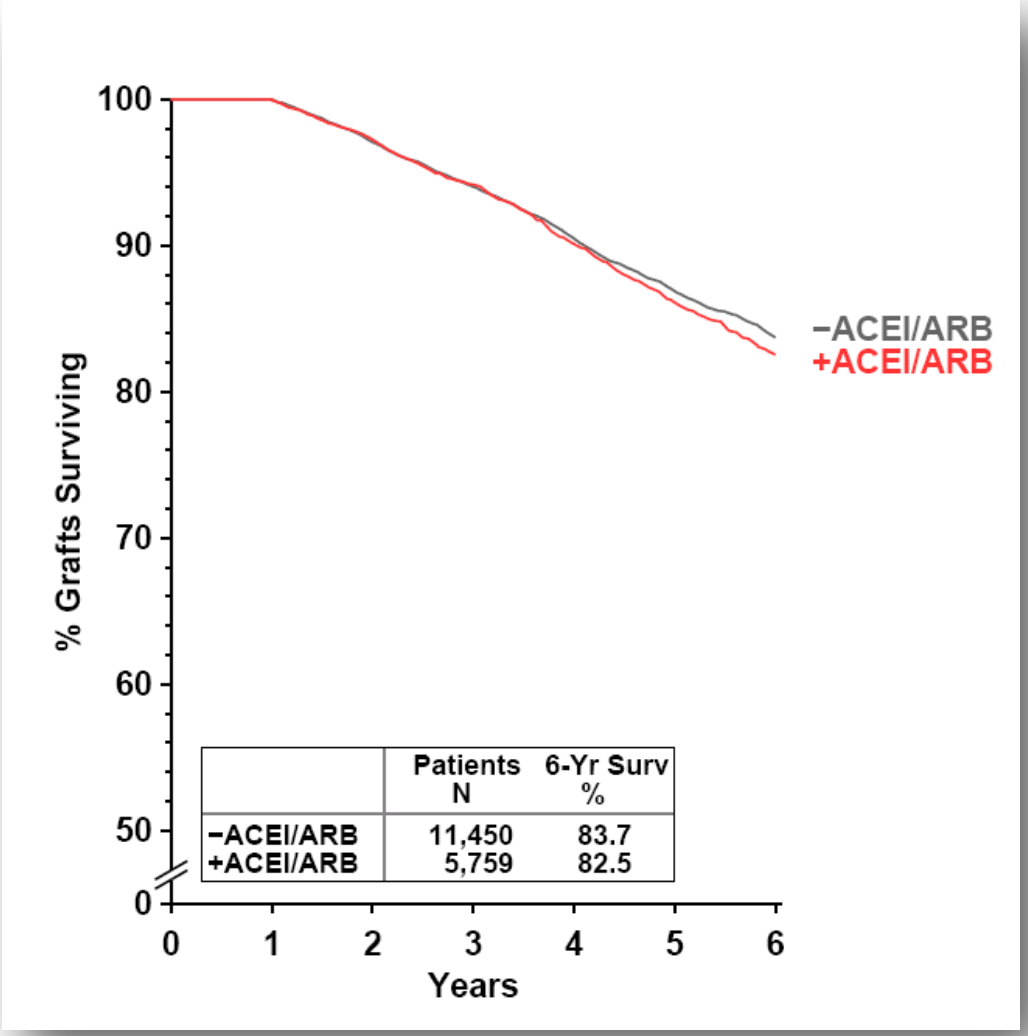
*Departments of *Transplantation Immunology and †Nephrology, University of Heidelberg, Heidelberg, Germany*

It was reported recently that treatment of kidney transplant recipients with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II type 1 receptor blockers (ARB) is associated with strikingly improved long-term graft and patient survival. This finding has important implications for future posttransplantation therapy recommendations. In an analysis of 17,209 kidney and 1744 heart transplant recipients, an association of treatment with ACEI/ARB with improved transplant outcome could not be confirmed. It is concluded that recommendations for a widespread use of ACEI/ARB treatment in transplant recipients are unwarranted.

J Am Soc Nephrol 17: 3257–3262, 2006

ACEI / ARB

First Kidney Transplants 1995–2004 (n=17,209)



J Am Soc Nephrol 17: 3257–3262, 2006

Lippincott Williams & Wilkins
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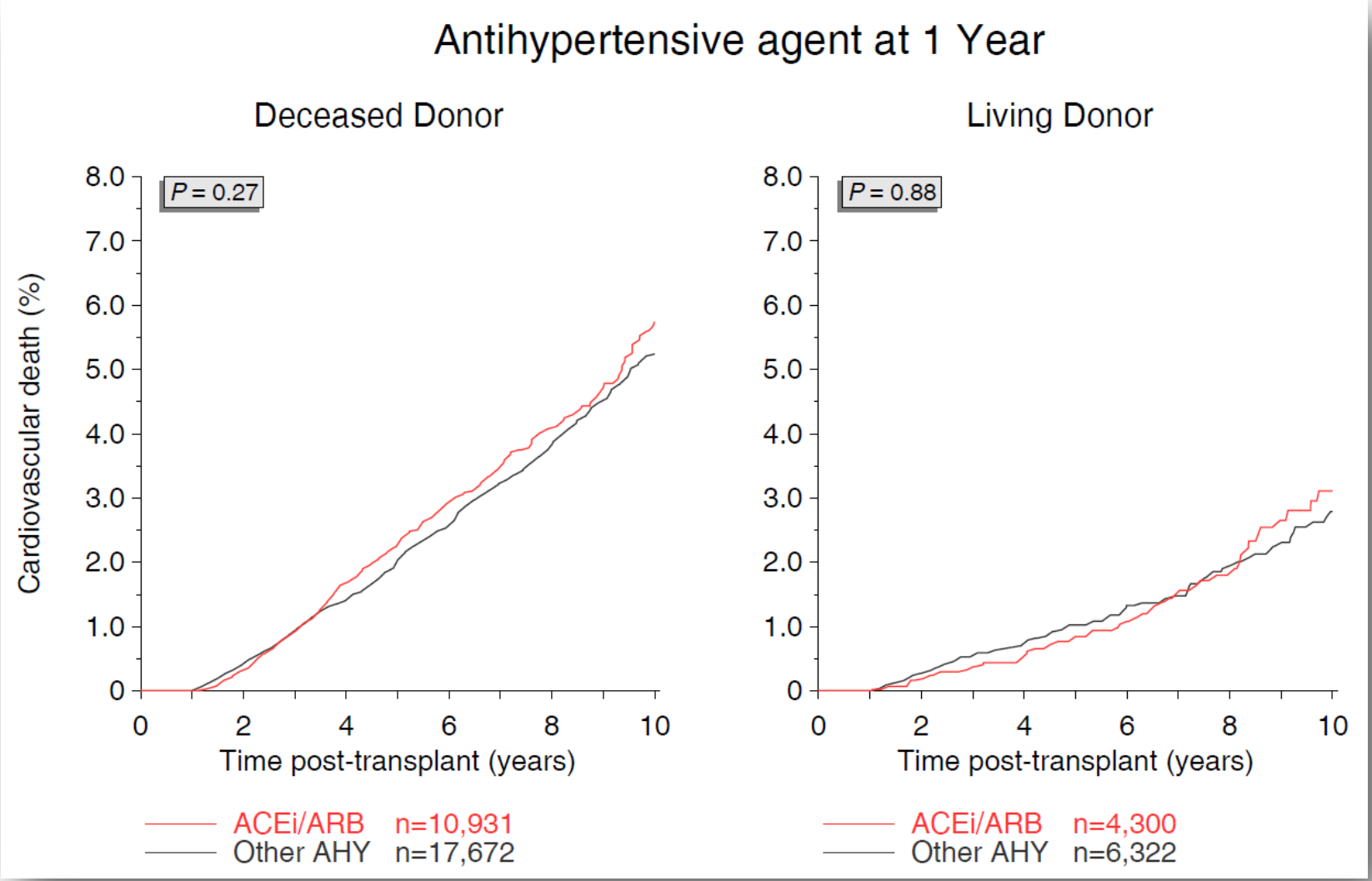

2009

LIPPINCOTT WILLIAMS & WILKINS
Transplantation
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SPECIAL FEATURES

Influence of Immunosuppressive Regimens on Graft Survival and Secondary Outcomes After Kidney Transplantation

Gerhard Opelz, and Bernd Döhler; for the Collaborative Transplant Study

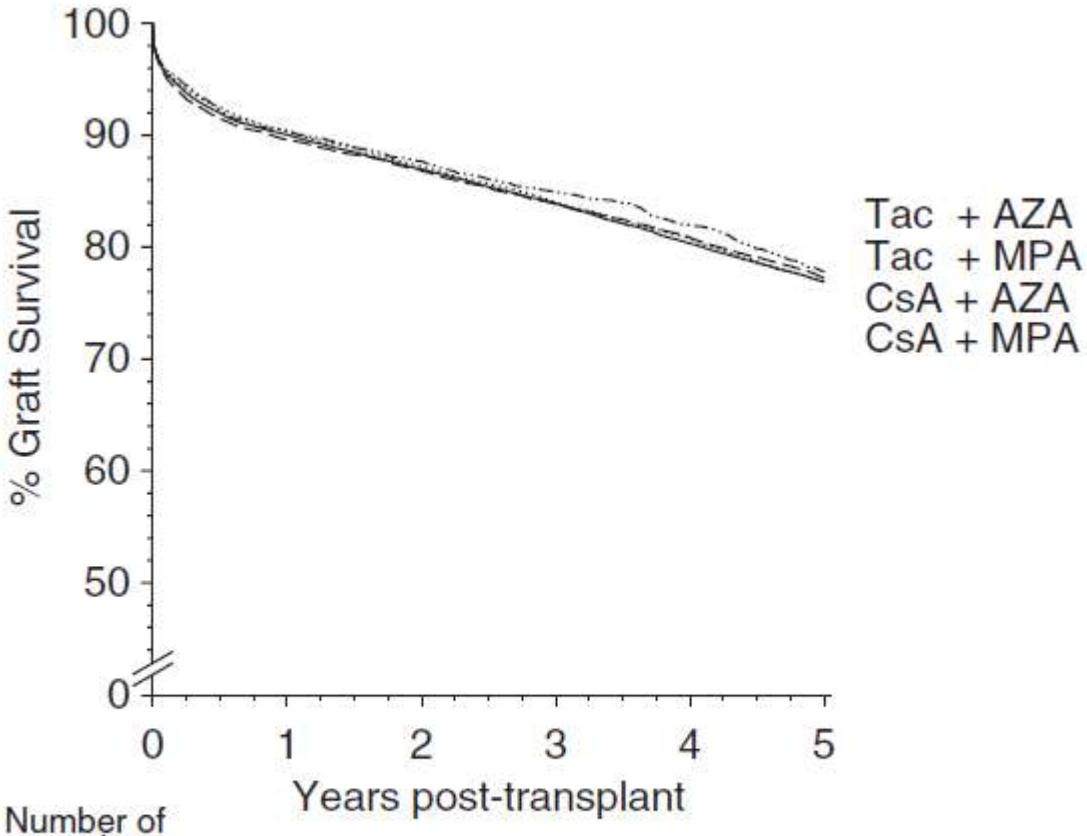
Background. There have been striking changes during the last 10 years concerning the choice of calcineurin inhibitor and antimetabolite agent prescribed after kidney transplantation.

Methods. A retrospective analysis of 51,303 patients undergoing deceased-donor kidney transplantation during 1998 to 2007 was performed using multivariate regression analysis. All patients received cyclosporine A (CsA) or tacrolimus (Tac) with azathioprine (AZA) or mycophenolic acid (MPA) on an intention-to-treat basis with corticosteroids plus/minus antibody induction. Graft survival rates and secondary outcomes were analyzed. A subanalysis was performed for transplants undertaken during 2002 to 2007, in which all patients were treated with MPA plus corticosteroids and CsA or Tac.

Results. All-cause graft failure and death-censored graft failure to 5 years posttransplant did not differ significantly between Tac and CsA. We found no evidence in support of previous claims that MPA results in superior long-term graft survival compared with AZA treatment. At the end of year 1, Tac was associated with a lower risk for serum creatinine more than or equal to 130 μmol/L ($P<0.001$) and hypercholesterolemia ($P<0.001$) versus CsA, but a higher risk for de novo posttransplant diabetes ($P<0.001$). MPA treatment was associated with a lower risk of acute rejection ($P<0.001$) but a higher risk of hospitalization because of infection ($P<0.001$) versus AZA.

Initial Immunsuppression 1998–2007

Deceased Donor Kidney Transplants

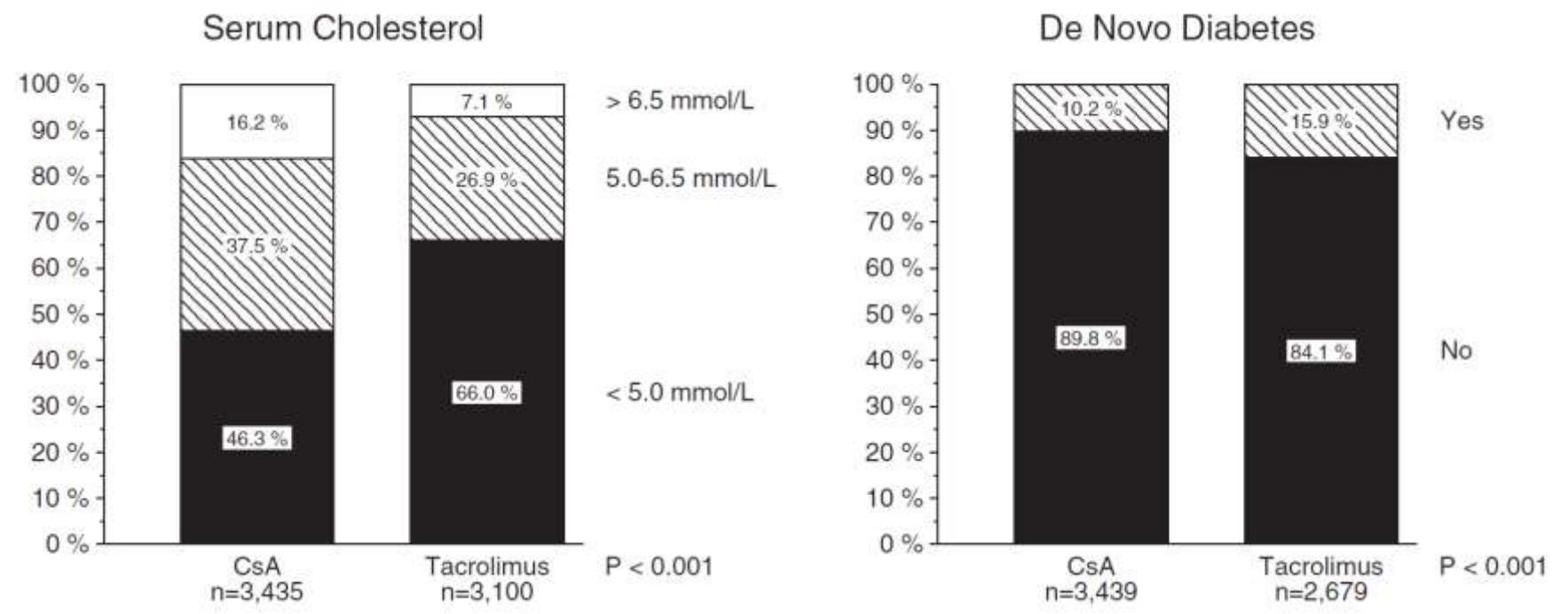


Number of transplants						
Tac + AZA	1,811	1,574	1,395	1,221	1,070	890
Tac + MPA	17,854	14,167	11,036	8,148	5,935	3,846
CsA + AZA	7,166	6,220	5,747	5,261	4,699	4,094
CsA + MPA	22,968	19,079	16,184	13,147	10,197	7,553

Transplantation 87: 795–802, 2009

Initial Immunsuppression 1998–2007

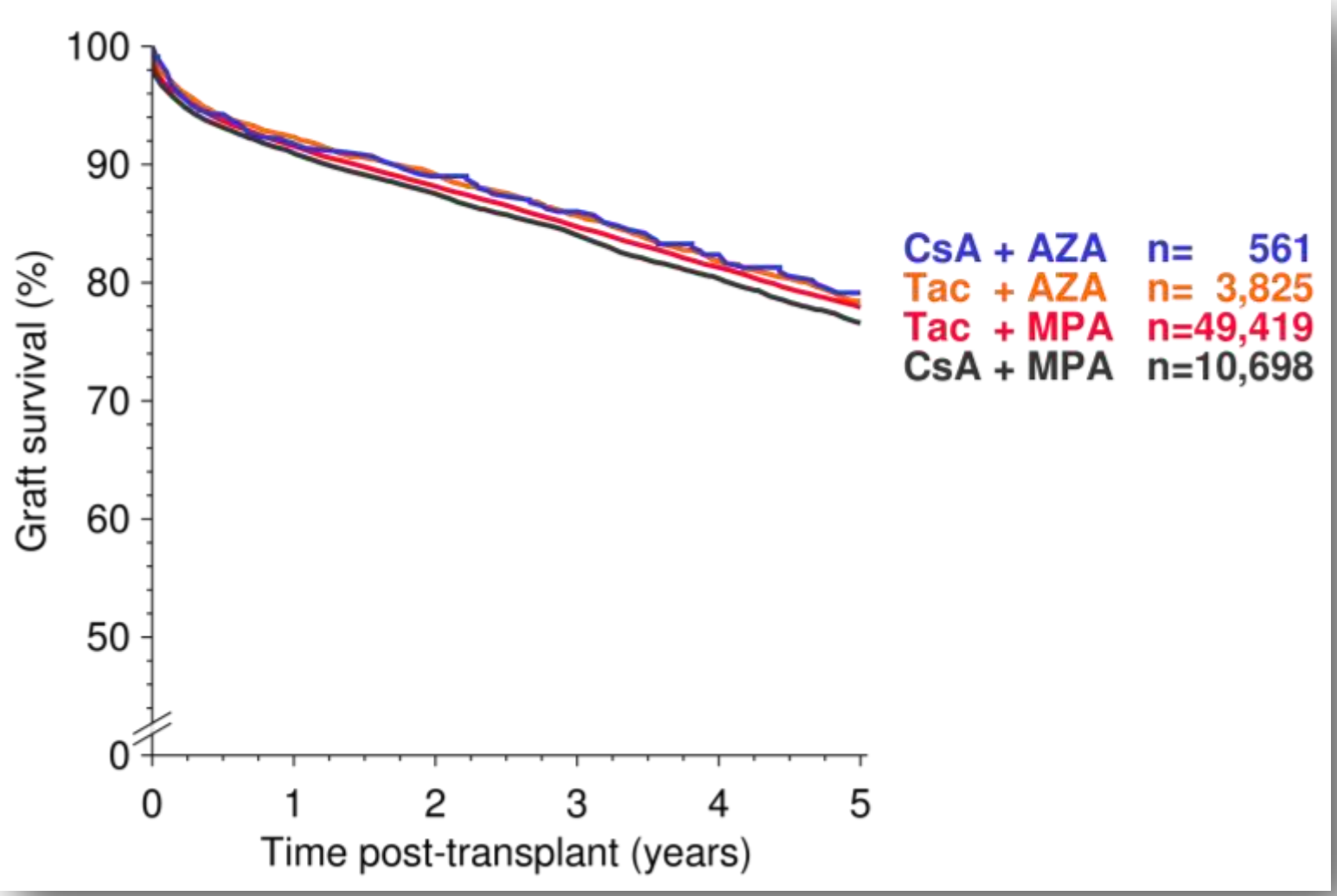
Deceased Donor Kidney Transplants



Transplantation 87: 795–802, 2009

Initial Immunsuppression 2008–2017

Deceased Donor Kidney Transplants



Transplantation 87: 795–802, 2009 (updated)

2005

American Journal of Transplantation
ASTO
ASTS
OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF TRANSPLANTATION AND THE AMERICAN SOCIETY OF TRANSPLANT SURGEONS

American Journal of Transplantation 2005; 5: 720–728
Blackwell Munksgaard

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doi: 10.1111/j.1600-6143.2004.00765.x

Long-Term Prospective Study of Steroid Withdrawal in Kidney and Heart Transplant Recipients

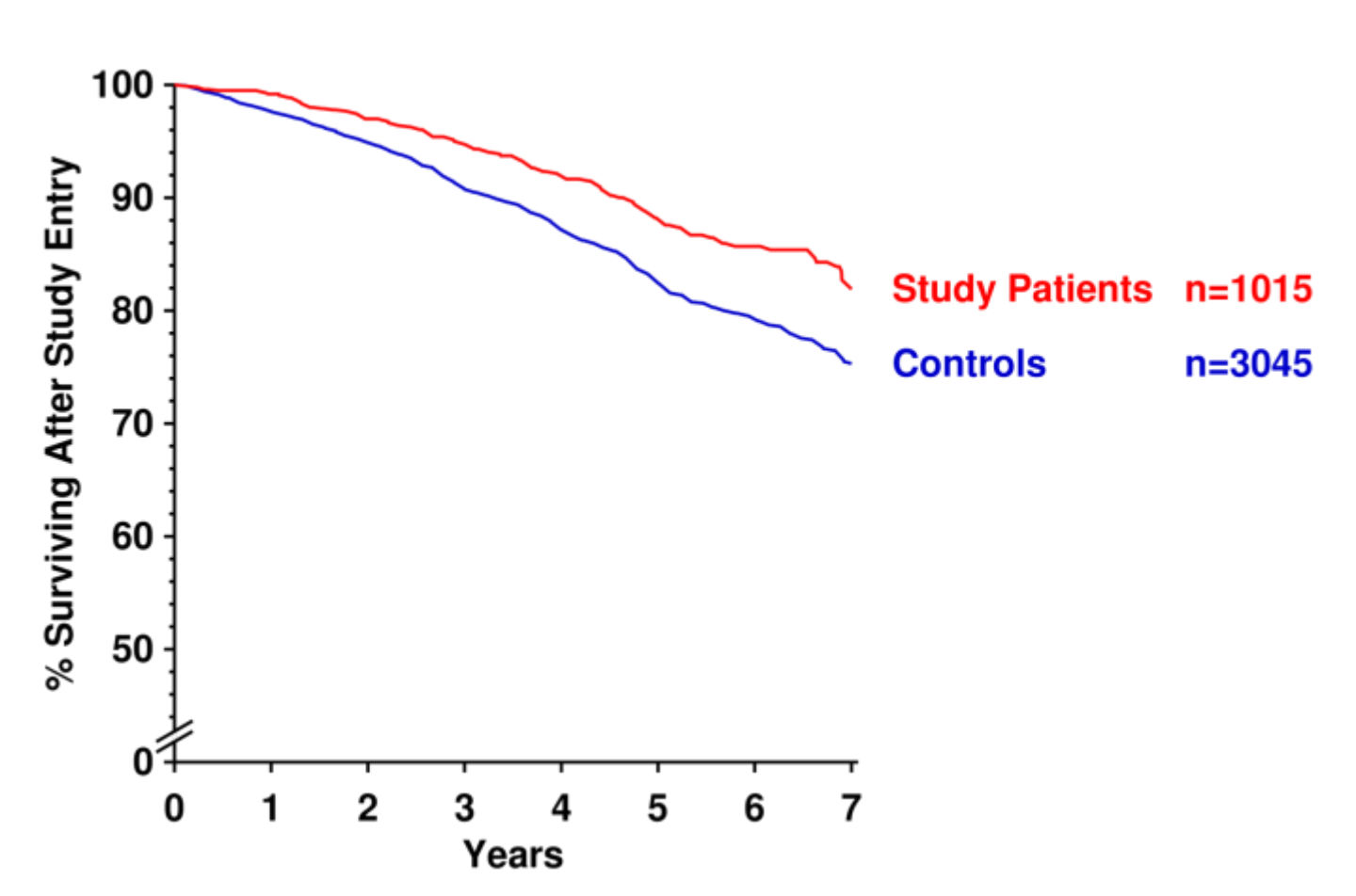
Gerhard Opelz, Bernd Döhler* and Gunter Laux for the Collaborative Transplant Study

Department of Transplantation Immunology, University of Heidelberg, Heidelberg, Germany
**Corresponding author: Gerhard Opelz, gerhard.opelz@med.uni-heidelberg.de*

pressive agents (1). Corticosteroids, which have been used for more than four decades, lead to side effects including weight gain, cataracts and bone loss, and also enhance cardiovascular risk factors such as hypertension, hyperlipidemia and diabetes (2). Although the advent of triple therapy with cyclosporine (CYA), steroids and azathioprine (AZA) has allowed steroid doses to be reduced, steroid-induced morbidity is still a major problem in transplant re-

Prospective Steroid Withdrawal Study

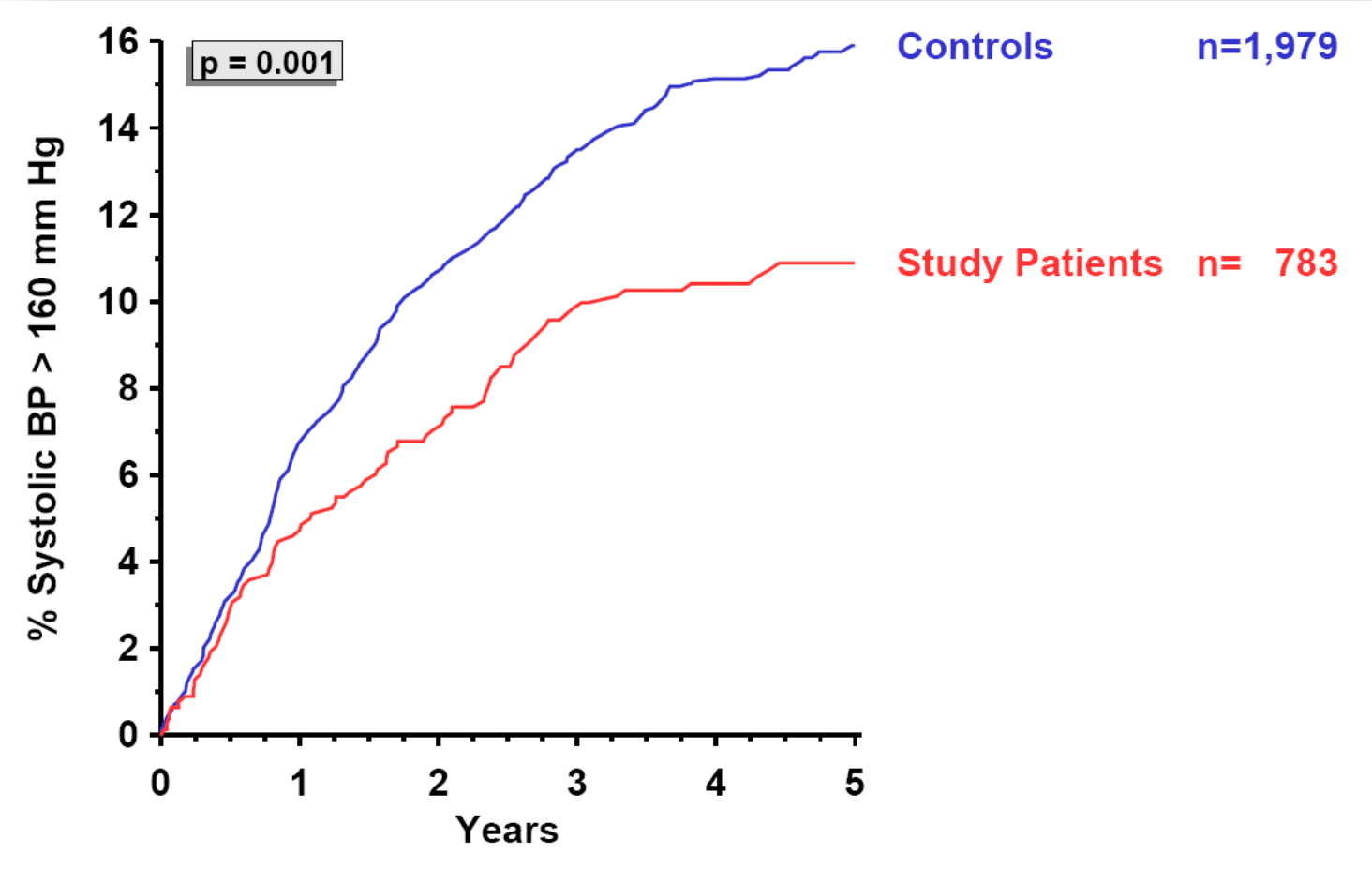
Deceased Donor Kidney Transplants



Am J Transplant 5: 720–728, 2005

Hypertension

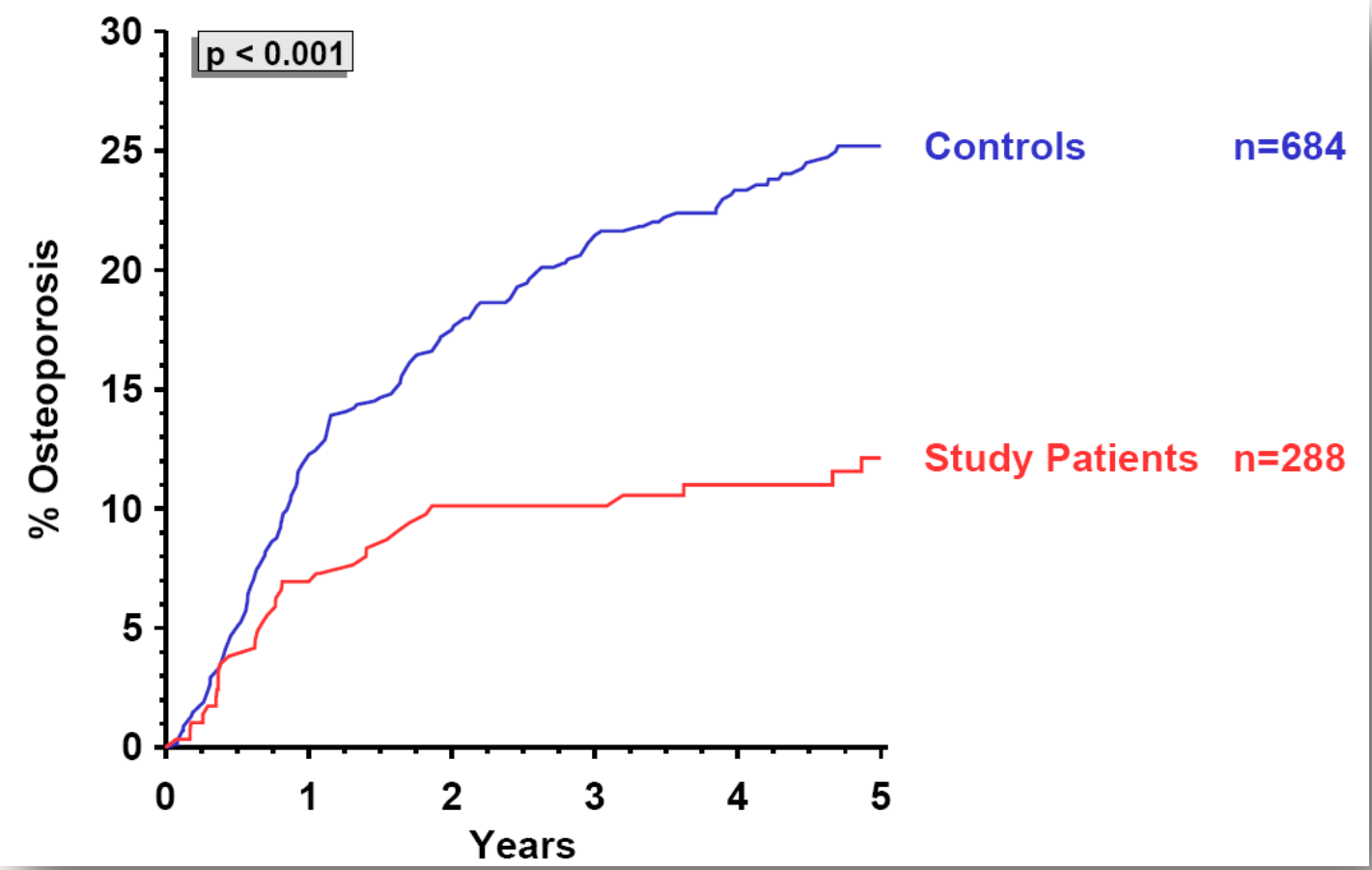
Prospective Steroid Withdrawal Study



Am J Transplant 5: 720–728, 2005

Osteoporosis

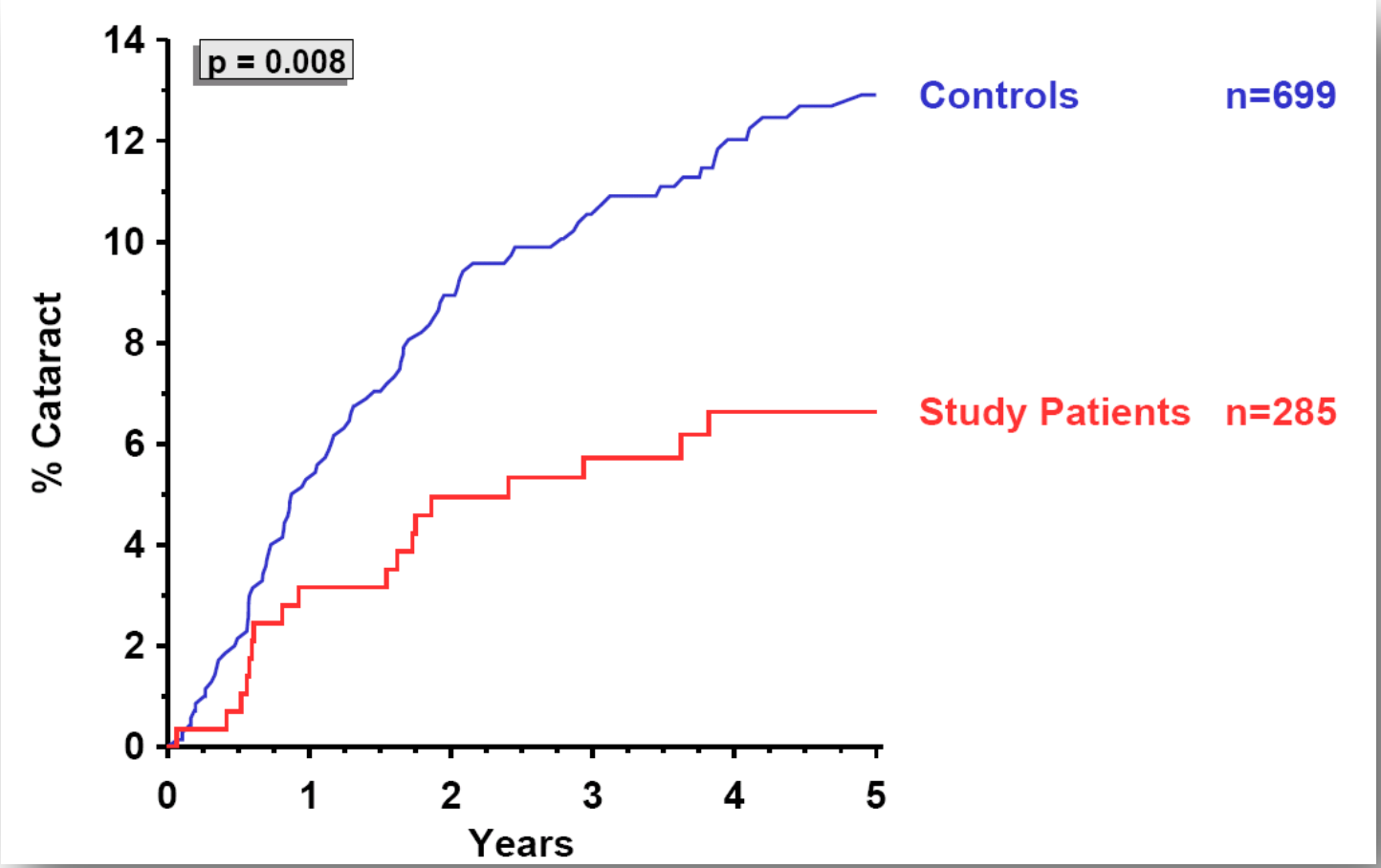
Prospective Steroid Withdrawal Study



Am J Transplant 5: 720–728, 2005

Cataract

Prospective Steroid Withdrawal Study



Am J Transplant 5: 720–728, 2005

2013

American Journal of Transplantation
ASTO
ASTS
OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF TRANSPLANTATION AND THE AMERICAN SOCIETY OF TRANSPLANT SURGEONS

American Journal of Transplantation 2013; 13: 2096–2105
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doi: 10.1111/ajt.12313

Association Between Steroid Dosage and Death With a Functioning Graft After Kidney Transplantation

G. Opelz* and B. Döhler

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**Corresponding author: Gerhard Opelz, gerhard.opelz@med.uni-heidelberg.de*

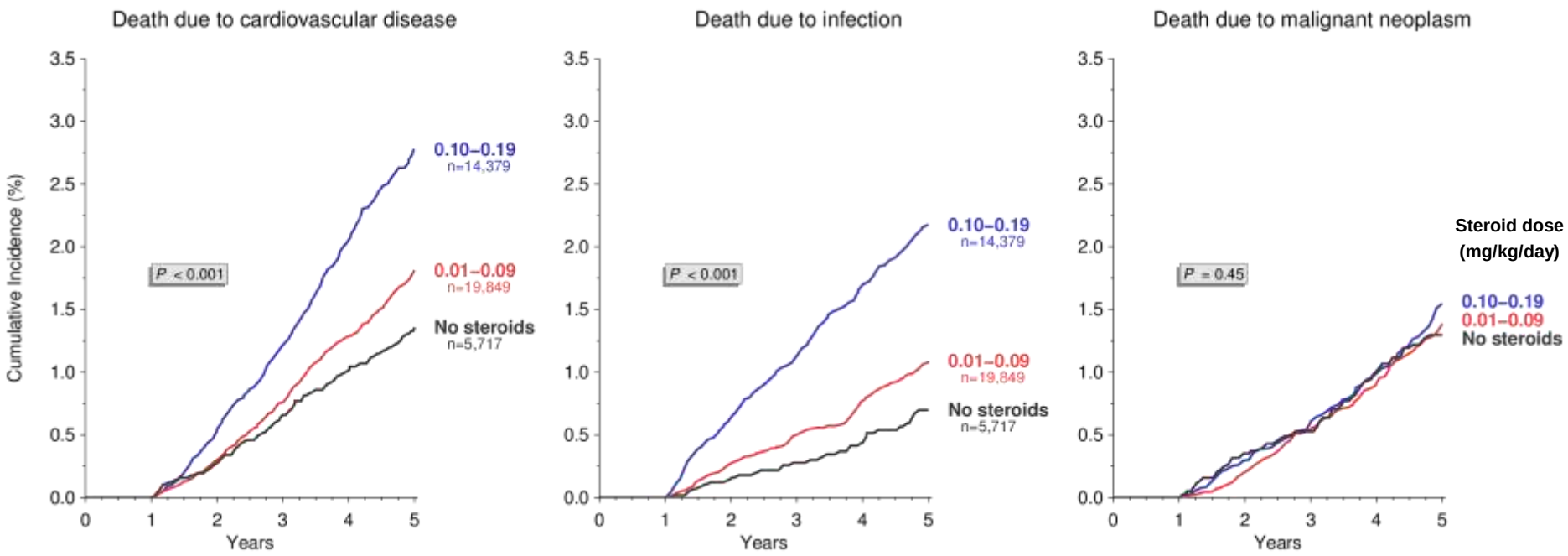
Death with a functioning graft remains a major challenge following kidney transplantation. Steroid dosing may be a modifiable risk factor. Collaborative

Introduction

As the incidence of acute rejection has declined after kidney transplantation (1), attention has transferred to improving long-term outcomes in kidney transplant recipients and, in particular, the high rate of death with a functioning graft. Death with function now occurs in 2–5% of patients each year (1,2), and is almost as frequent as graft failure after the first year posttransplant (3). The most common reason for death in patients with a functioning graft is cardiovascular disease, followed by infection and malignancy (1,2,4,5), and targeting these causes is a key clinical priority.

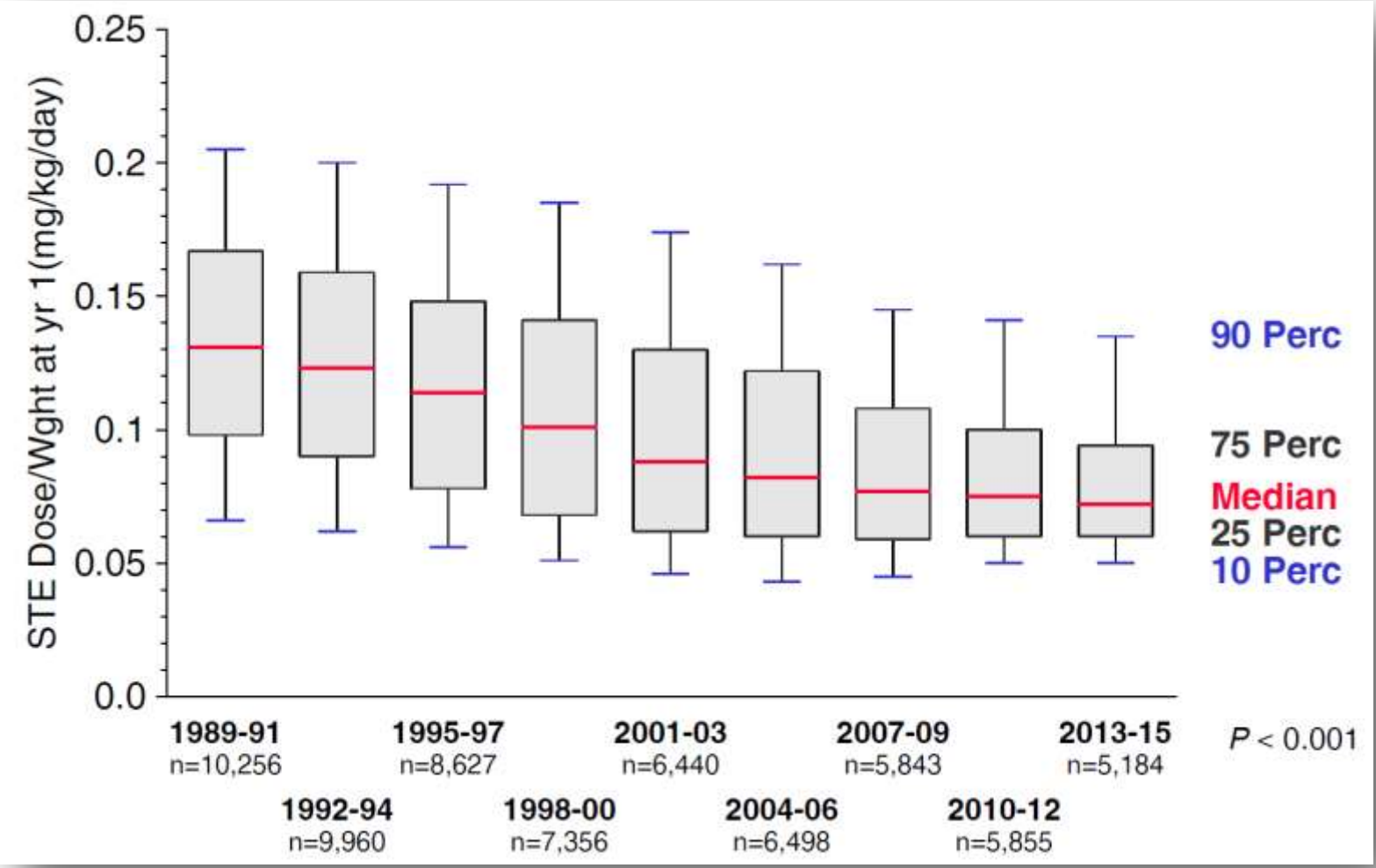
Death with Functioning Graft

Deceased Donor Kidney Transplants 1995–2010, Adults



Am J Transplant 13: 2096–2105, 2013

1-Year Steroid Dose



2008

LIPPINCOTT WILLIAMS & WILKINS
Transplantation
THE OFFICIAL JOURNAL OF THE TRANSPLANTATION SOCIETY

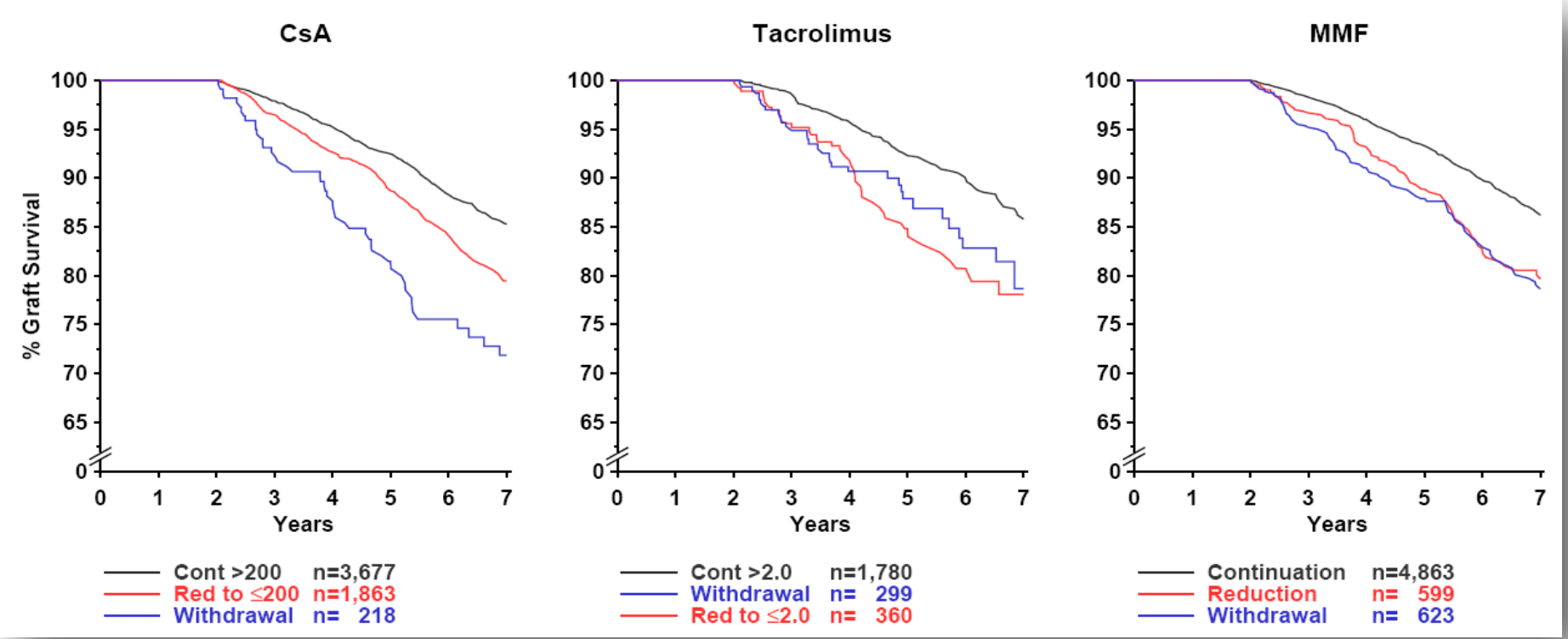
SPECIAL FEATURE

Effect on Kidney Graft Survival of Reducing or Discontinuing Maintenance Immunosuppression After the First Year Posttransplant

Gerhard Opelz and Bernd Döhler

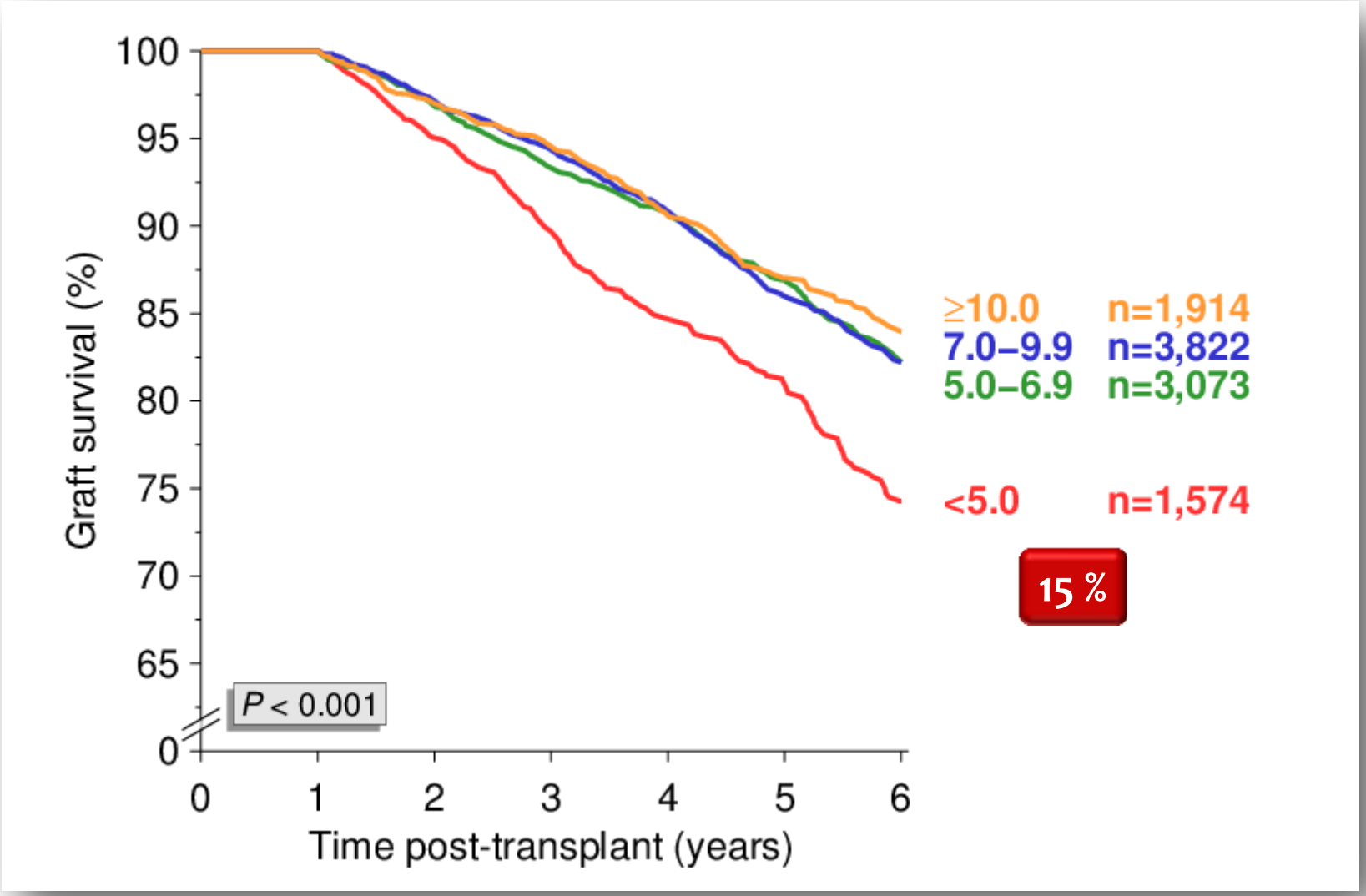
Background. Data are scarce concerning the impact of maintenance immunosuppression dose reductions posttransplant.
Methods. Graft survival according to dose reduction or discontinuation of calcineurin inhibitors or mycophenolate mofetil (MMF) after the first year posttransplant was evaluated in 25,045 patients undergoing kidney transplantation during 1996 to 2005. No patient in this analysis had experienced a rejection and all had good graft function before dose reduction.
Results. Reduction of cyclosporine (CsA) dose to less than or equal to 150 mg/day, tacrolimus to less than or equal to 2 mg/day, or MMF to less than or equal to 1.0 g/day in patients on CsA or less than or equal to 0.5 g/day in patients on tacrolimus during the second year posttransplant was associated with a statistically significant reduction in graft survival (hazard ratios between 1.37 and 1.65). Withdrawal of CsA, tacrolimus, or MMF during year 2 was also associated with an increase in the risk of graft loss compared with continuing treatment (hazard ratio 1.52–1.73).
Conclusions. This observational analysis indicates that in kidney transplant patients with good graft function, withdrawing maintenance CsA, tacrolimus or MMF, or reducing the dose of these agents below certain thresholds after the first year posttransplant is associated with a significant risk of graft loss.

Dose Reduction or Withdrawal



Transplantation 86: 371–376, 2008

Tacrolimus 1-Year Trough Level (ng/ml)



2013

LIPPINCOTT WILLIAMS & WILKINS
Transplantation
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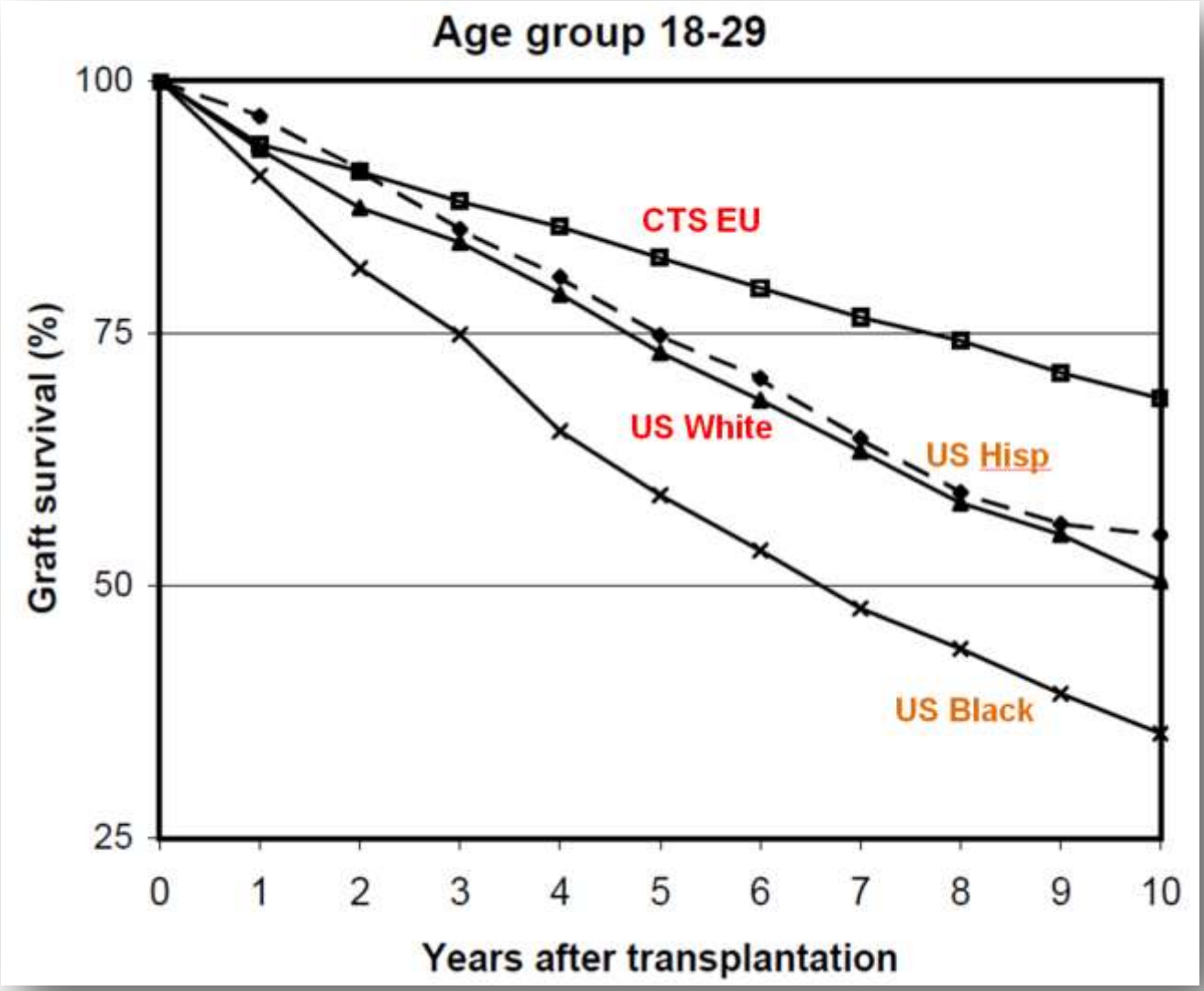
SPECIAL FEATURES

Kidney Graft Survival in Europe and the United States: Strikingly Different Long-Term Outcomes

Adam Gondos,[1,3] Bernd Döhler,[2] Hermann Brenner,[1] and Gerhard Opelz[2]

Background. Kidney graft survival has never been systematically compared between Europe and the United States. **Methods.** Applying period analysis to first deceased-donor (DD) and living-donor kidney grafts from the United Network for Organ Sharing/Organ Procurement and Transplantation Network for the United States and the Collaborative Transplant Study for Europe, we compared overall and age-specific 1-, 5-, and 10-year graft survival for Europeans and white, African, and Hispanic Americans for the 2005 to 2008 period. A Cox regression model was used to adjust for differences in patient characteristics.

Europe vs. United States



Transplantation 95: 267–274, 2013

Short time survival has improved, but ...

Matas 2007 “there has not been a parallel improvement in the long-term outcome”

Marcén et al. 2010 “there has been little or no improvement in late allograft failure”

Legendre et al. 2014 “the long-term results have improved either minimally or not at all”

Gaetano et al. 2016 “no similar improvement in long-term graft survival has been observed”

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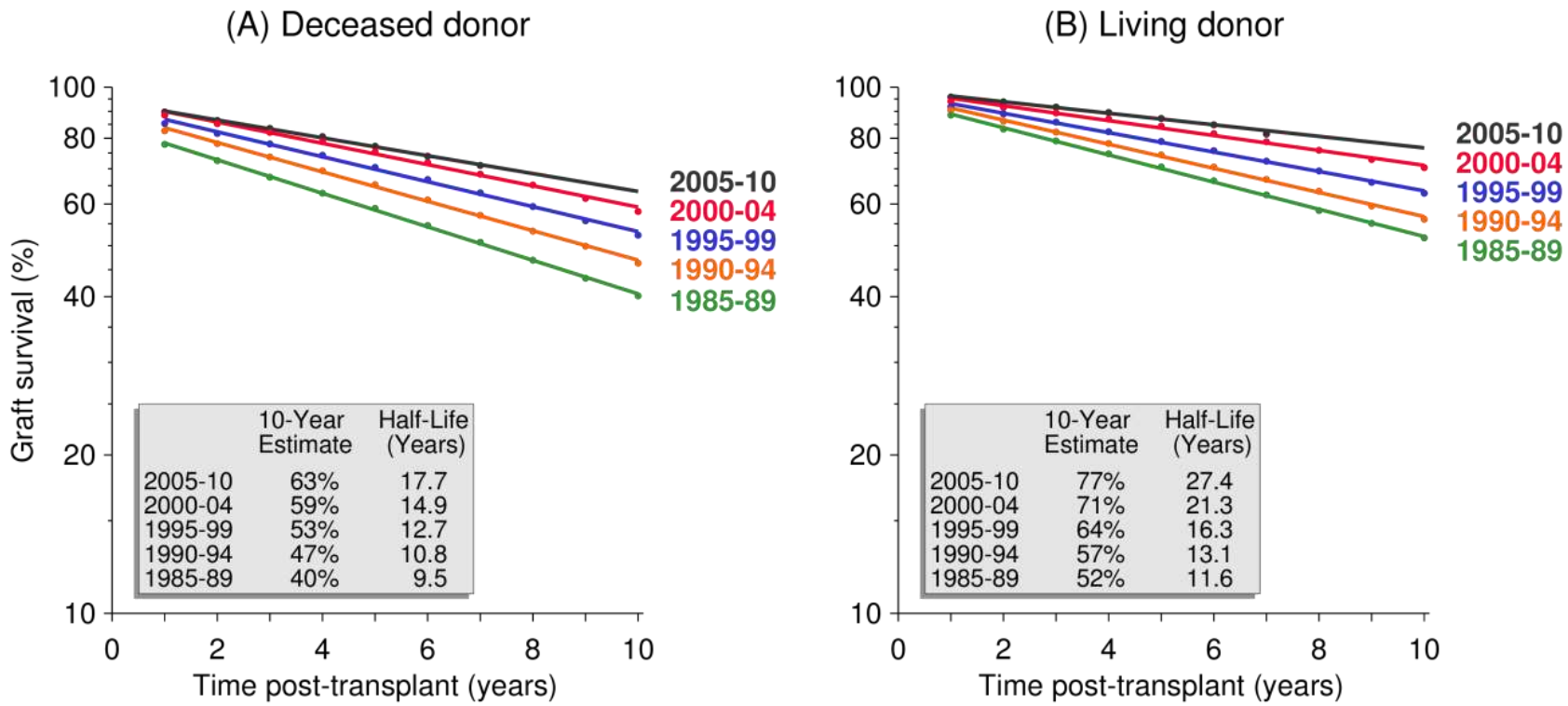

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CLINICAL AND TRANSLATIONAL RESEARCH

Reduced Rate of Cardiovascular Death After Cytomegalovirus Prophylaxis in Renal Transplant Recipients

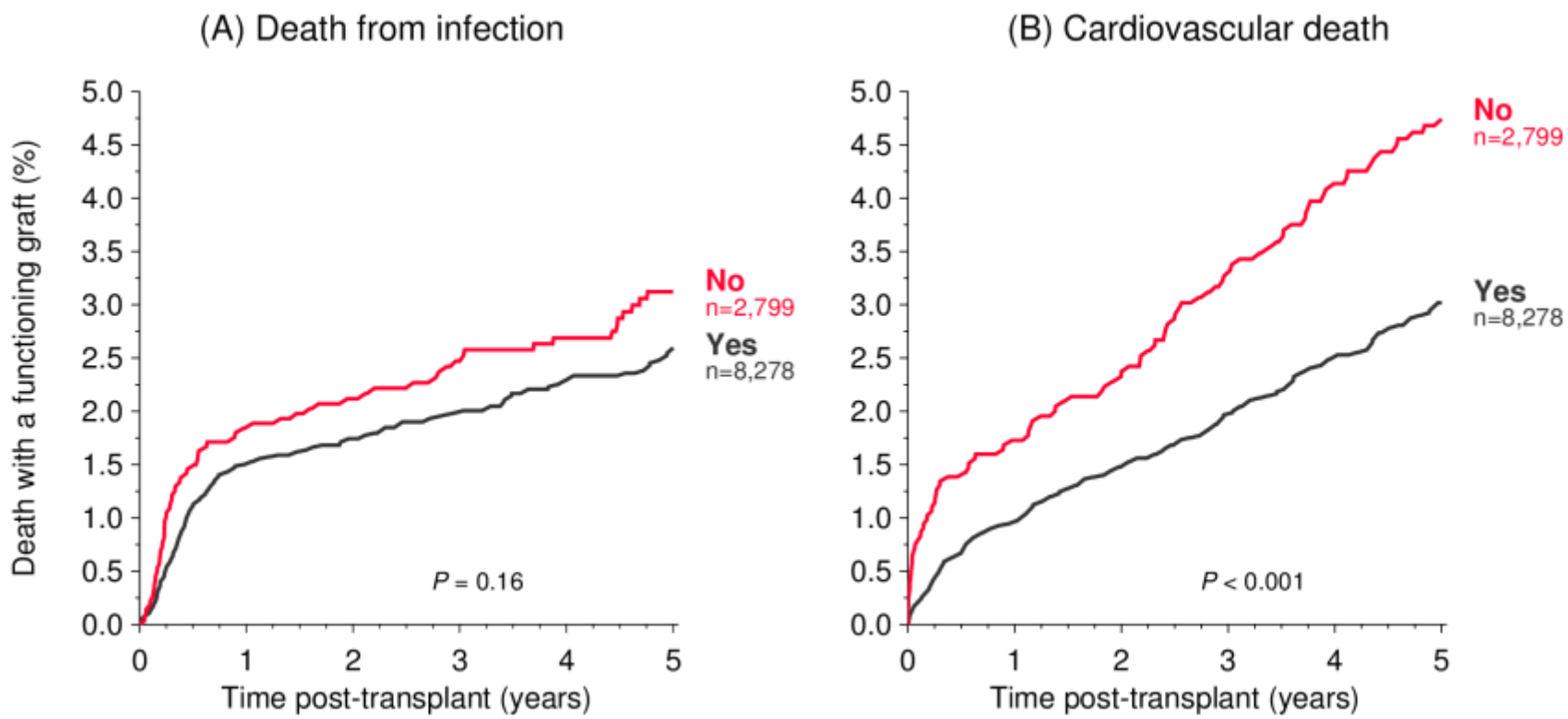
Gerhard Opelz[1,2] and Bernd Döhler[1]

Background. It is unknown how death with a functioning graft (DWFG) is affected in renal transplant recipients who receive prophylaxis for cytomegalovirus (CMV) infection.
Methods. Data from 61,927 adult recipients of a deceased donor kidney transplant in 1990 to 2012 registered with the Collaborative Transplant Study were analyzed.
Results. Cytomegalovirus prophylaxis was administered in 18%, 75%, 27% and 34% of R−/D− (recipient-negative, donor-negative), R−/D+, R+/D− and R+/D+ transplants, respectively. Only in R−/D+ transplants was CMV prophylaxis associated with significantly improved patient survival versus no prophylaxis ($P<0.001$). Unexpectedly, in the R−/D+ subgroup, DWFG because of infection was not significantly affected by use of CMV prophylaxis ($P=0.16$) but death from cardiovascular disease was significantly lower ($P<0.001$). Cox regression analysis confirmed that the primary impact of CMV prophylaxis on DWFG in R−/D+ transplants was because of reduced cardiovascular death (hazard ratio, 0.66; 95% confidence interval, 0.51–0.85; $P=0.002$), an effect restricted to patients aged 40 years or older (hazard ratio, 0.61; 95% confidence interval, 0.46–0.81; $P<0.001$).
Conclusion. We conclude that CMV prophylaxis is associated with a significant benefit for risk of cardiovascular DWFG among R−/D+ kidney transplant patients aged ≥40 years. Cytomegalovirus prophylaxis appears particularly critical in this patient subpopulation.

Transplantation 99: 1197–1202, 2015

CMV Prophylaxis

Recipient CMV–, Donor CMV+



Transplantation 99: 1197–1202, 2015

2002

JASN® Journal of the American Society of Nephrology

J Am Soc Nephrol 13: 1650–1656, 2002

Identification of Highly Responsive Kidney Transplant Recipients Using Pretransplant Soluble CD30

CANER SÜSAL, STEFFEN PELZL, BERND DÖHLER, and GERHARD OPELZ for the Collaborative Transplant Study

Department of Transplantation Immunology, Institute of Immunology, University of Heidelberg, Heidelberg, Germany.

Pre-Transplant sCD30

Deceased Donor Kidney Transplants

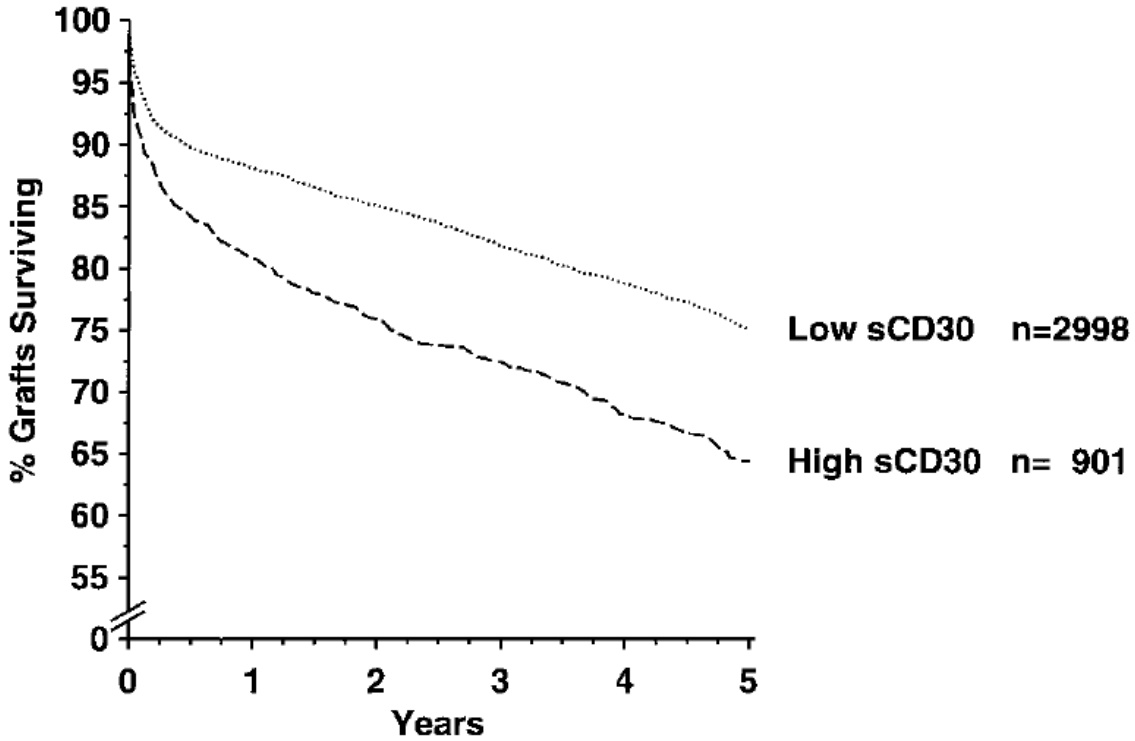
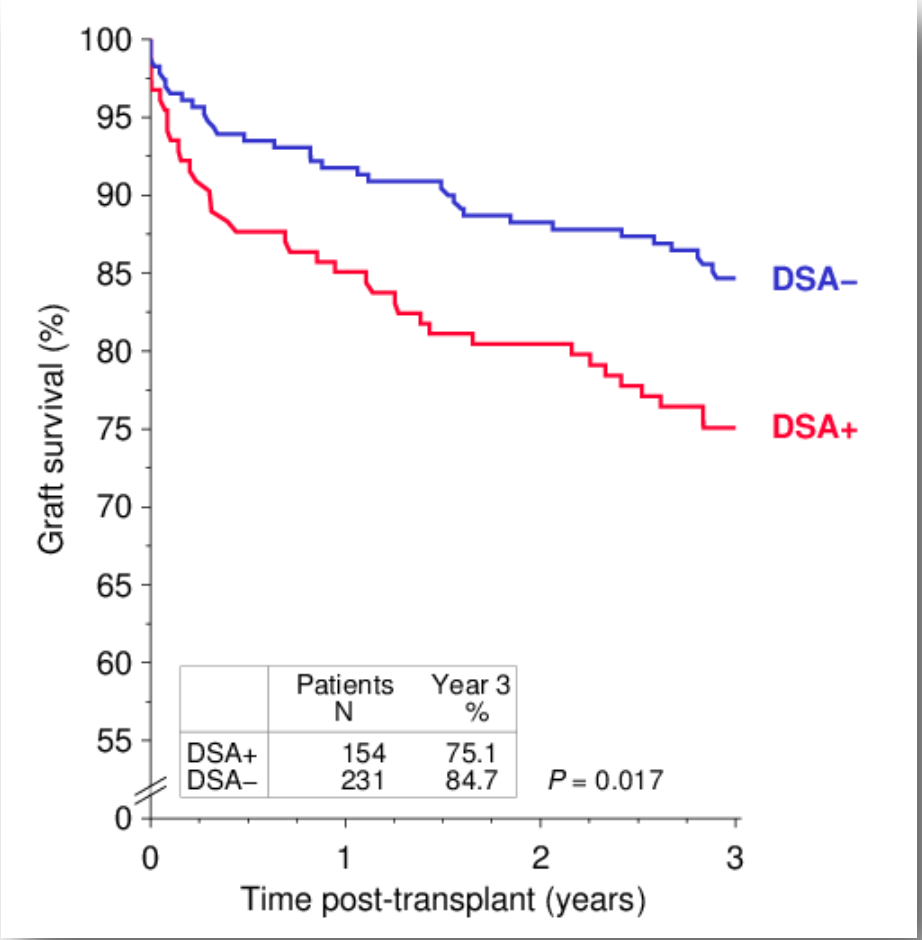


Figure 1. Association of soluble CD30 (sCD30) content in pretransplant serum with cadaver kidney graft survival. Recipients with low serum sCD30 had a significantly better graft survival rate than recipients with high sCD30 ($P < 0.0001$). Numbers of patients studied are indicated.

J Am Soc Nephrol 13: 1650–1656, 2002

Pre-Transplant DSA

DSA = Donor Specific Antibodies



Süsal, unpublished

2016

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EBioMedicine 9 (2016) 366–371

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journal homepage: www.ebiomedicine.com

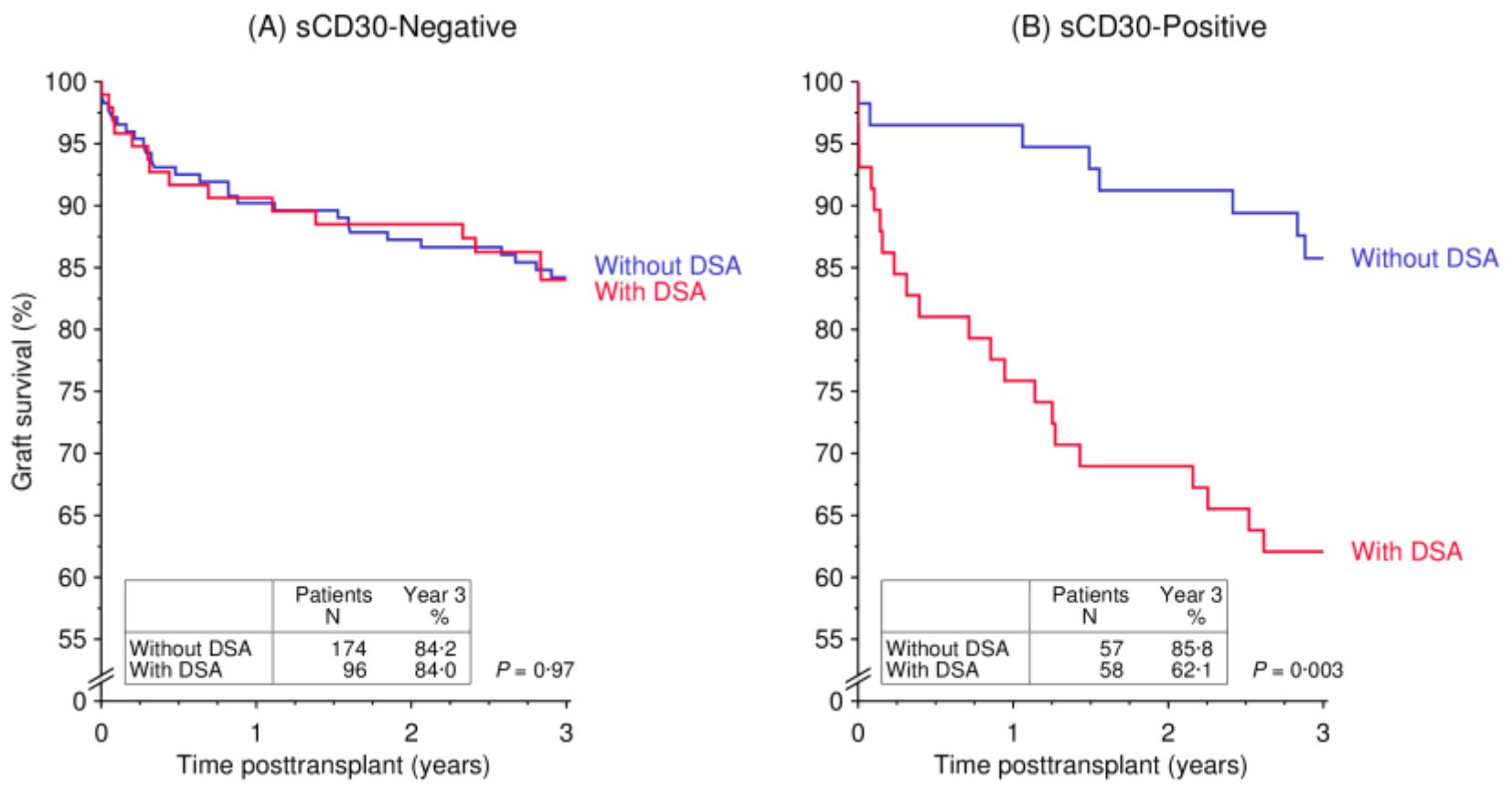
Research Paper

Donor-specific antibodies require preactivated immune system to harm renal transplant

Caner Süsal [a,*], Bernd Döhler [a], Andrea Ruhenstroth [a], Christian Morath [b], Antonij Slavcev [c], Thomas Fehr [d], Eric Wagner [e,q], Bernd Krüger [f], Margaret Rees [g], Sanja Balen [h], Stela Živčić-Ćosić [h], Douglas J. Norman [i], Dirk Kuypers [j], Marie-Paule Emonds [k], Przemyslaw Pisarski [l], Claudia Bösmüller [m], Rolf Weimer [n], Joannis Mytilineos [o], Sabine Scherer [a], Thuong H. Tran [a], Petra Gombos [a], Peter Schemmer [p], Martin Zeier [b], Gerhard Opelz [a], A Collaborative Transplant Study Report:

Pretransplant DSA and sCD30

Presensitized Deceased Donor Kidney Transplants



EBioMedicine 9: 366–371, 2016

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