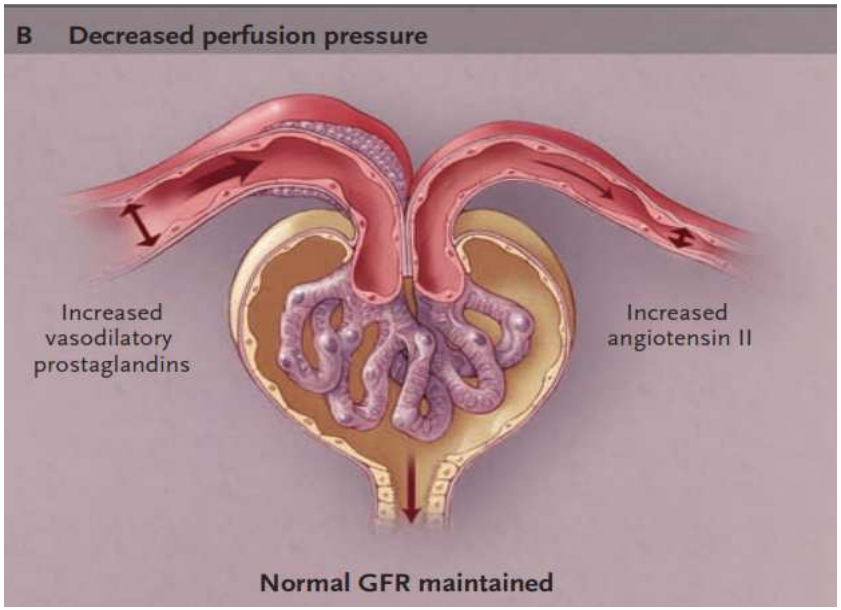
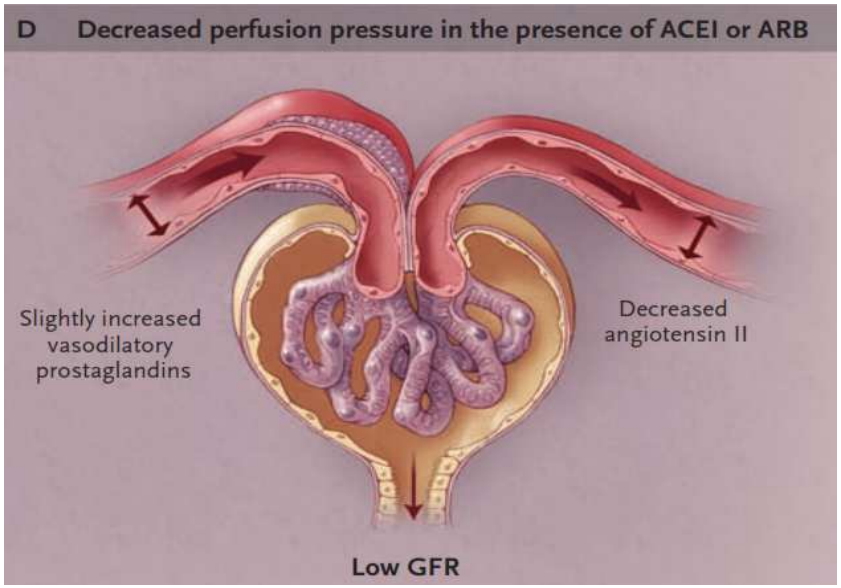
RAAS-Blockade nach Nierentransplantation – sinnvoll oder nicht ?





Hermann Haller und Christos Chatzikyrkou
Klinik für Nieren- und Hochdruckerkrankungen
Medizinische Hochschule Hannover

Hypertonie-Probleme nach Nierentransplantation

Bluthochdruck ist häufig nach Nierentransplantation

transplantierte Patienten sind Patienten mit CKD
zusätzlich blutdrucksteigernde Medikamente

Interaktionen mit der Immunsuppression/anderen Medikamenten

wird die Niere gefährdet ?
nützt es der transplantierten Niere ?

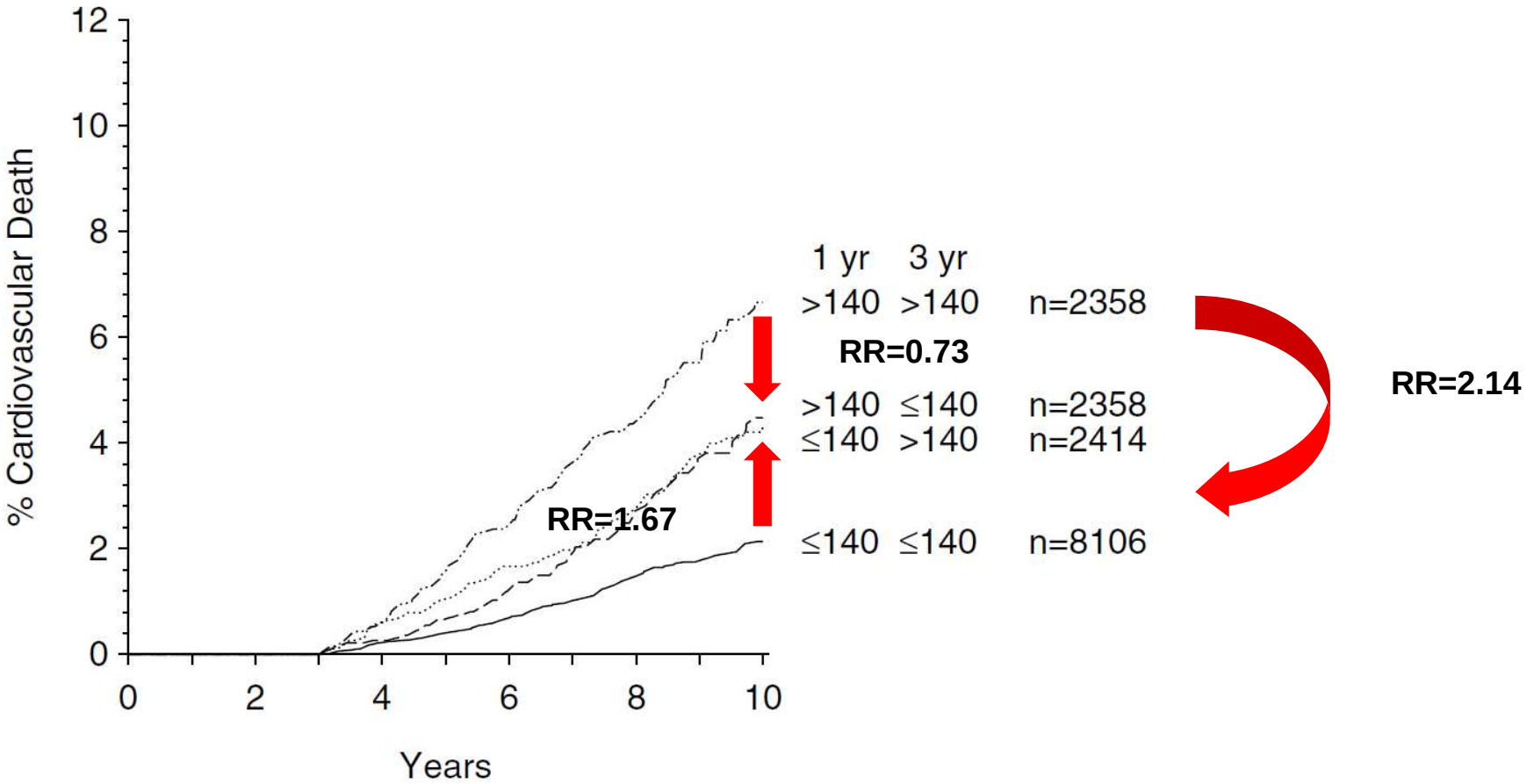
unmittelbar nach Tx/ langfristige Therapie-Strategie

welcher Zielblutdruck ist sinnvoll nach Tx ?

Sind alle Patienten gleich ? Kardiovaskuläres Risiko!
Sind alle Nieren gleich ?

Welche Antihypertensiva kann/soll man verwenden ?
RAAS-Blockade – sinnvoll oder nicht ??

Blutdruckkontrolle verbessert Transplantat- und Patientenüberleben: CTS Datenbank



Opelz & Döhler AJT 2005;5:2725-31

Zielblutdruckwerte (vor SPRINT)

Guideline	Uncomplicated Hypertension	CKD	Diabetes	Renal Transplant
JNC 8, 2014[a]	≥140/90	≥140/90	>140/90	n/d
ESH/ESC, 2013[c]	≥140/90	≥140/90	>140/90	n/d
KDIGO, 2009[e], 2012[d]	n/d	≥140/90	>130/80[b]	>130/80
	n/d	≥130/80[b]	>130/80[b]	

Weir et al. J Am Soc Nephrol 26: 1248–1260, 2015

KDIGO Richtlinien 2009

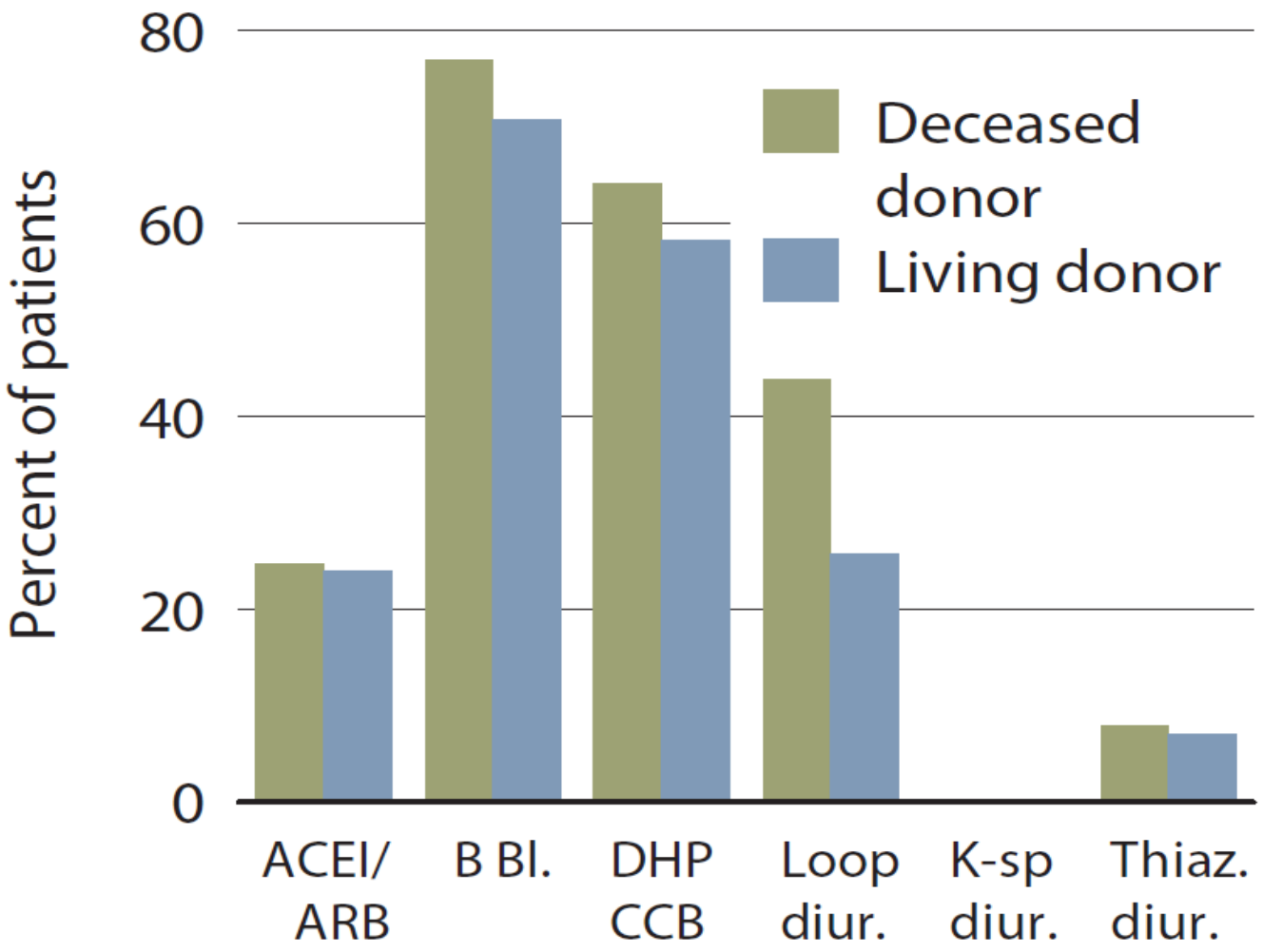
16.1.2: We suggest maintaining blood pressure at <130 mm Hg systolic and <80 mm Hg diastolic if ≥18 years of age, and <90th percentile for sex, age, and height if <18 years old. *(2C)*

16.1.3: To treat hypertension *(Not Graded)*:

- use any class of antihypertensive agent;
- monitor closely for adverse effects and drug–drug interactions; and
- when urine protein excretion ≥1 g/day for ≥18 years old and ≥600 mg/m^2/24 h for <18 years old, consider an ACE-I or an ARB as first-line therapy.

Am J Transplant 2009;9 (S3):S1-S155

Welche antihypertensiven Medikamente werden 6 Monate nach der Transplantation eingesetzt ?



US Renal Data 2011 Annual Report

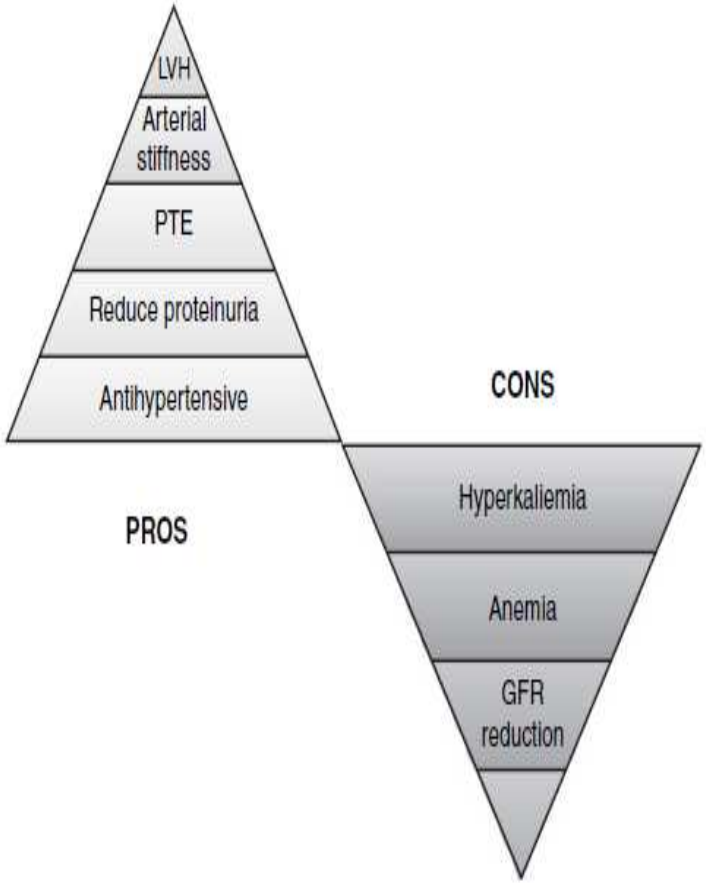
Welche antihypertensiven Medikamente werden nach der Transplantation eingesetzt ?
Cochrane Report von 2009

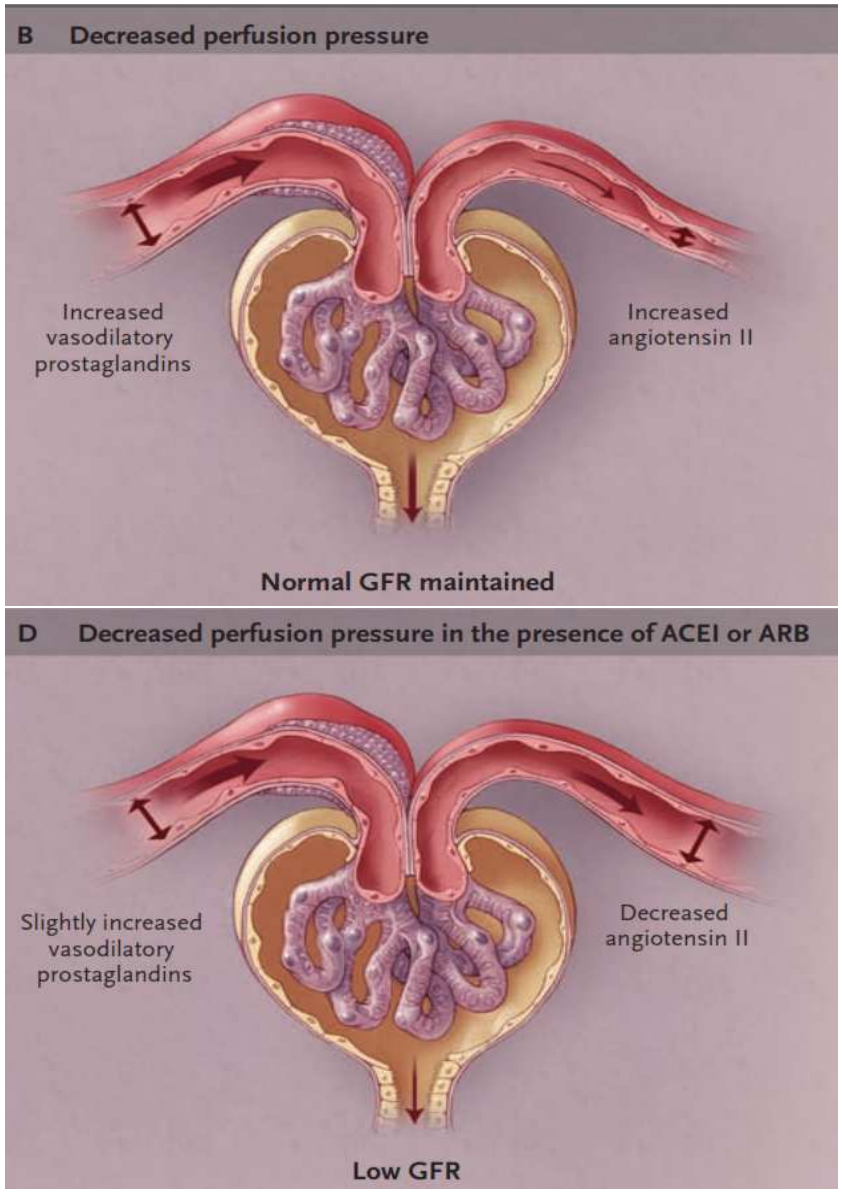
insgesamt 60 Studien, 3802 Patienten.
29 Studien CCB vs. Placebo (2262 Patienten
10 Studien ACEi vs. Placebo (445 Patienten)
7 Studien CCB vs. ACEi (405 Patienten)

„ These data suggest that CCB may be preferred as first line agents for hypertensive kidney transplant recipients. ACEi have some detrimental effects in kidney transplant recipients. More high quality studies reporting patient centred outcomes are required.“

Cross et al. Cochrane Database Syst Rev. 2009 Jul 8;(3)

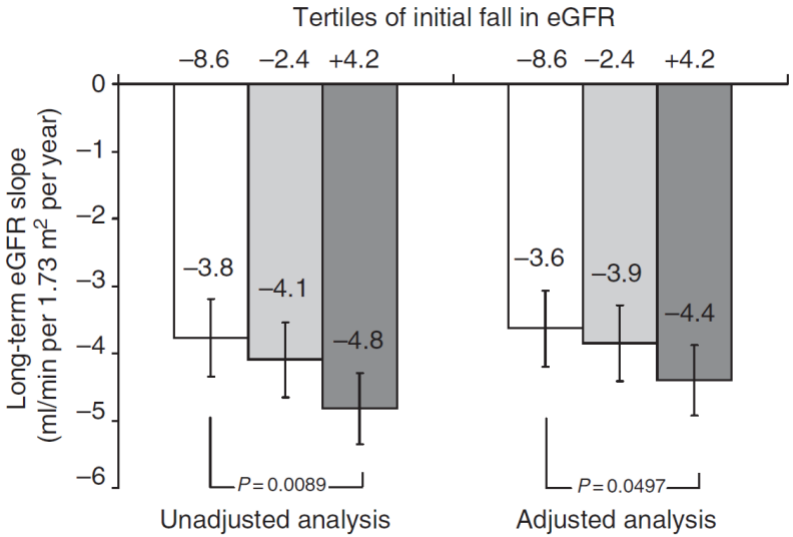
RAAS Blockade und Nierentransplantation

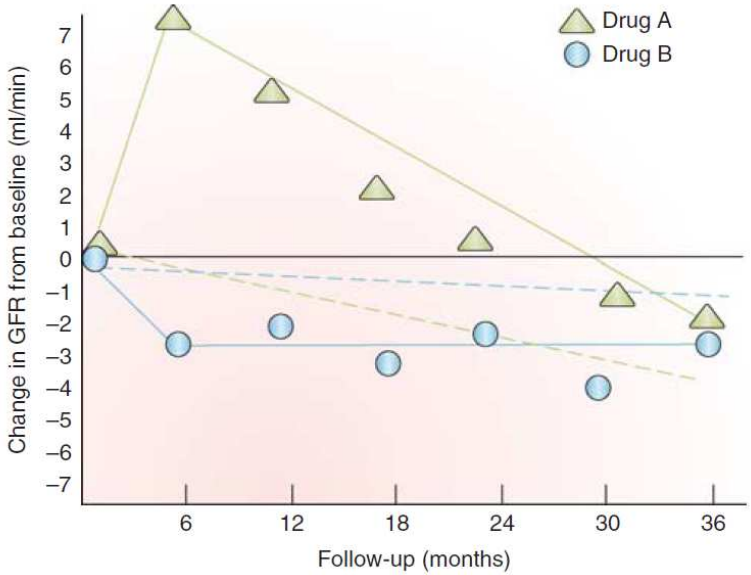




Cruzado et al Transpl Int 2008;21:304-13, Gary J Abuelo NEJM 2007;357:797-805

Der akute GFR Abfall nach RAAS Blockade ist assoziiert mit einem langfristig langsameren Verlust der Nierenfunktion

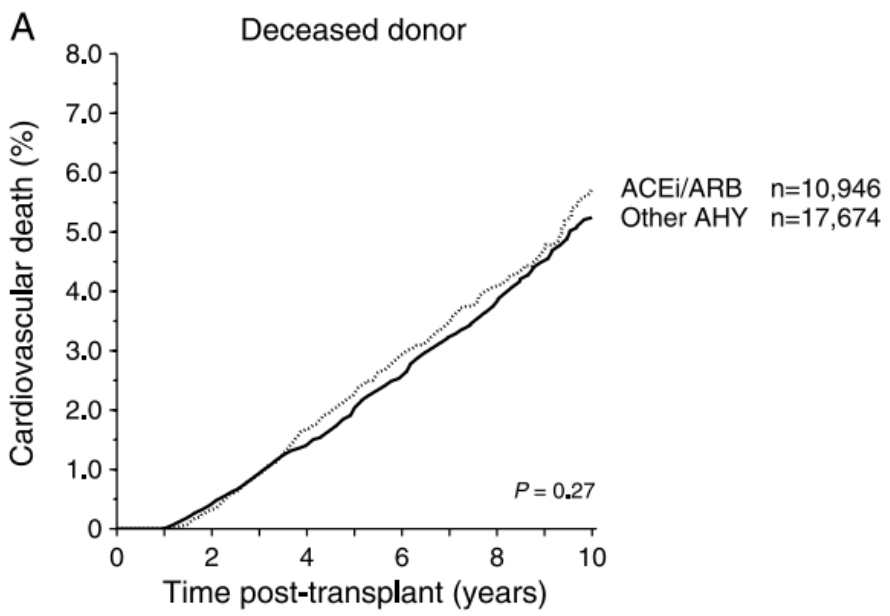


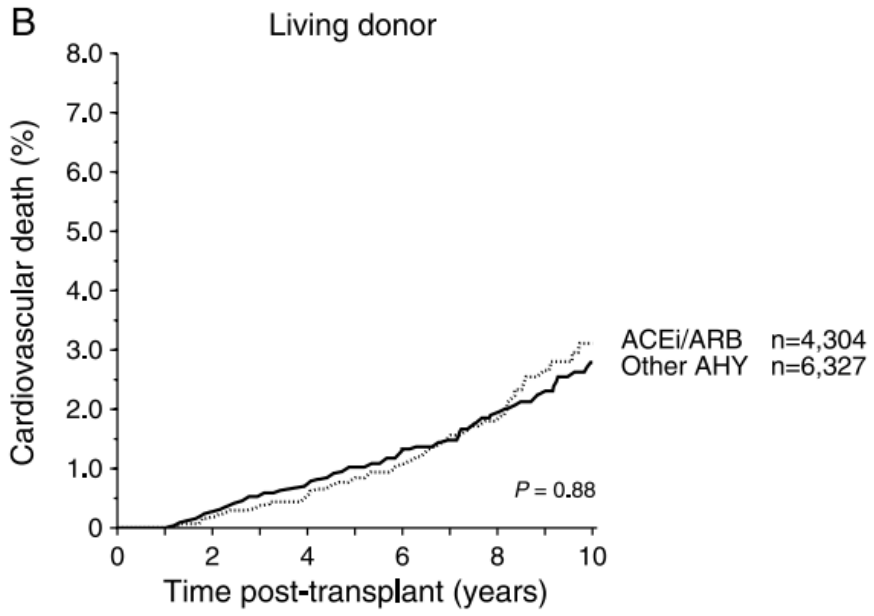


- **RENAAL Studie**
- **1500 Patienten, 3.4 Jahre follow up**

Holtkamp et al. Kidney Int 2011; 80:282-87
Matthew R Weir Kidney Int 2011;80:235-37

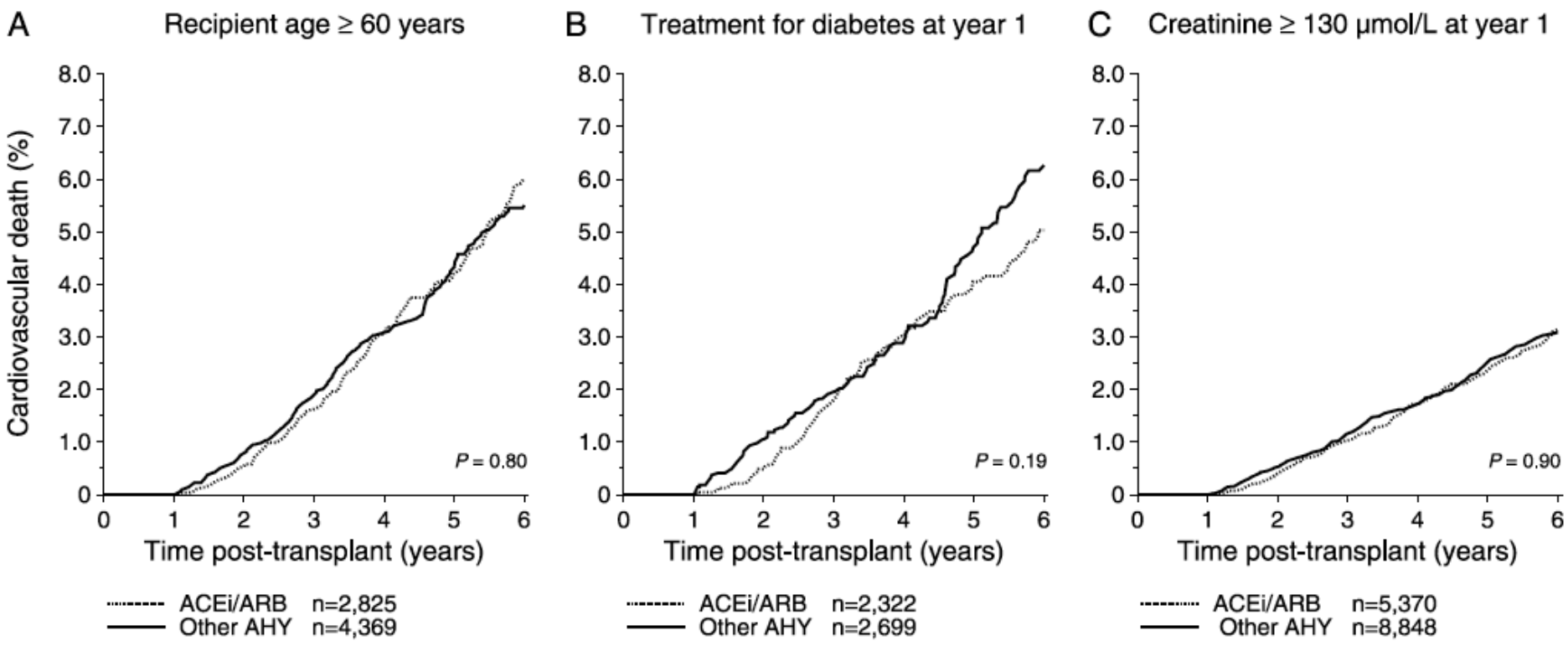
Effekte der RAAS Blockade auf das Transplant- und Patientenüberleben
(CTS Studie, 40.000 Patienten, 10 Jahre follow up)





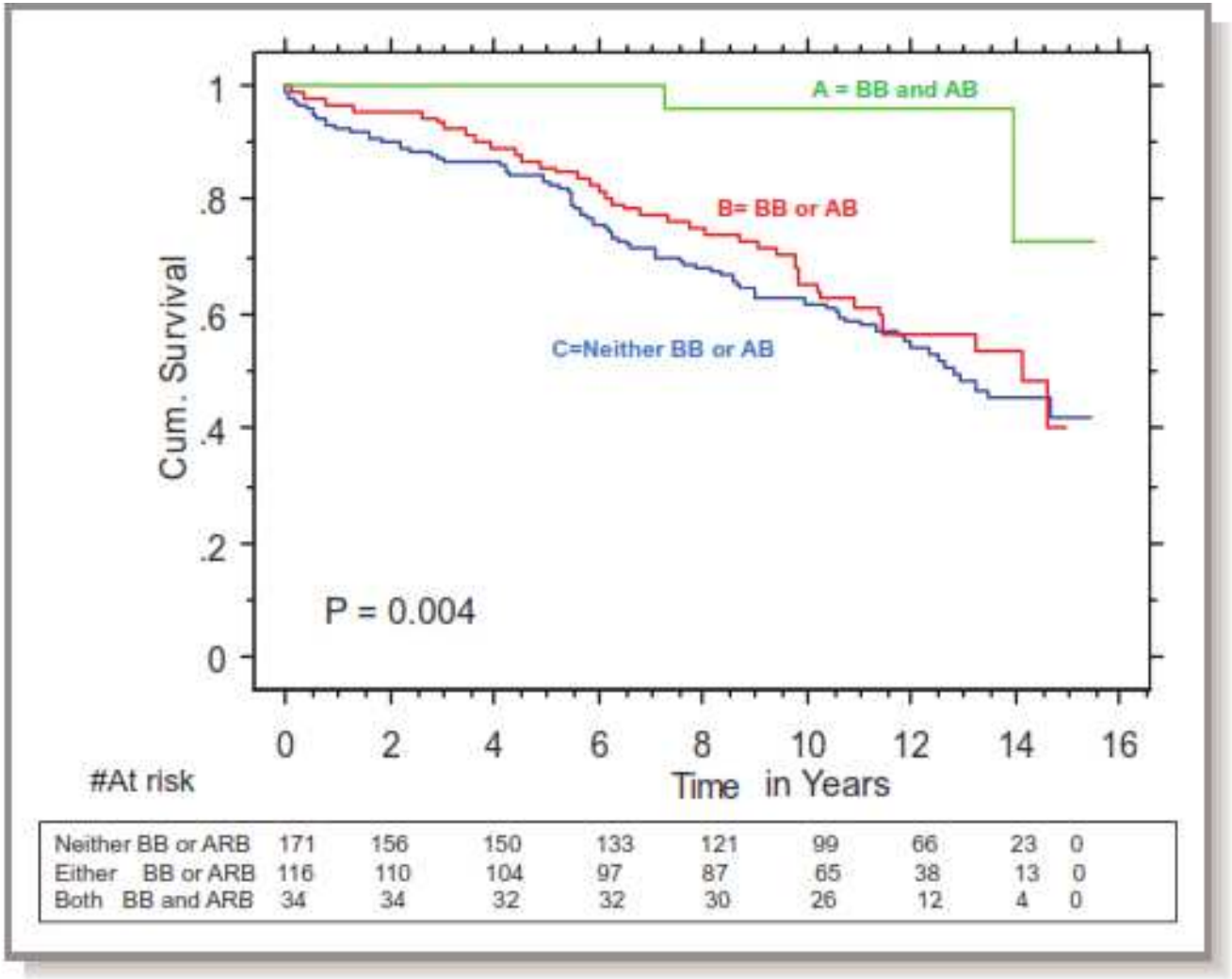
Opelz G and Döhler B Transplantation 2013

Neutrale Effekte der RAAS Blockade auf das Transplant- und Patientenüberleben (CTS Studie, 40.000 Patienten, 10 Jahre follow up)



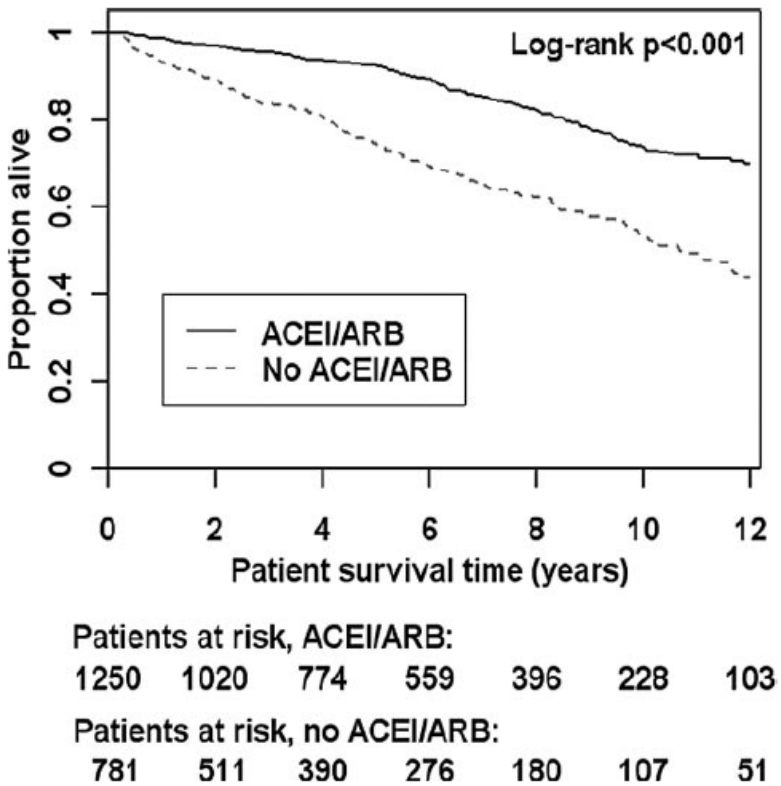
Opelz G and Döhler B Transplantation 2013

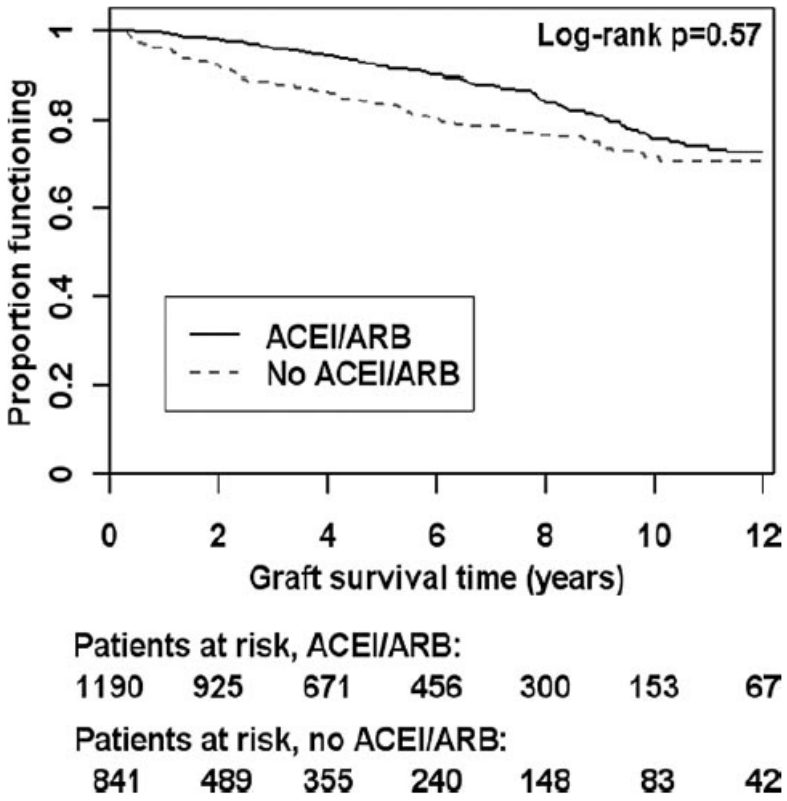
Positive Effekte der RAAS Blockade vor allem in Kombination mit Betablockade auf das Patientenüberleben (monozentrisch, retrospektiv, 320 Patienten)



Aftab W et al, JAHA 2013

Positive Effekte der RAAS Blockade nur auf das Patientenüberleben
(2000 Patienten, monozentrisch, 3,5 Jahre follow up)





Heinze et al, JASN 2006;17:889-899

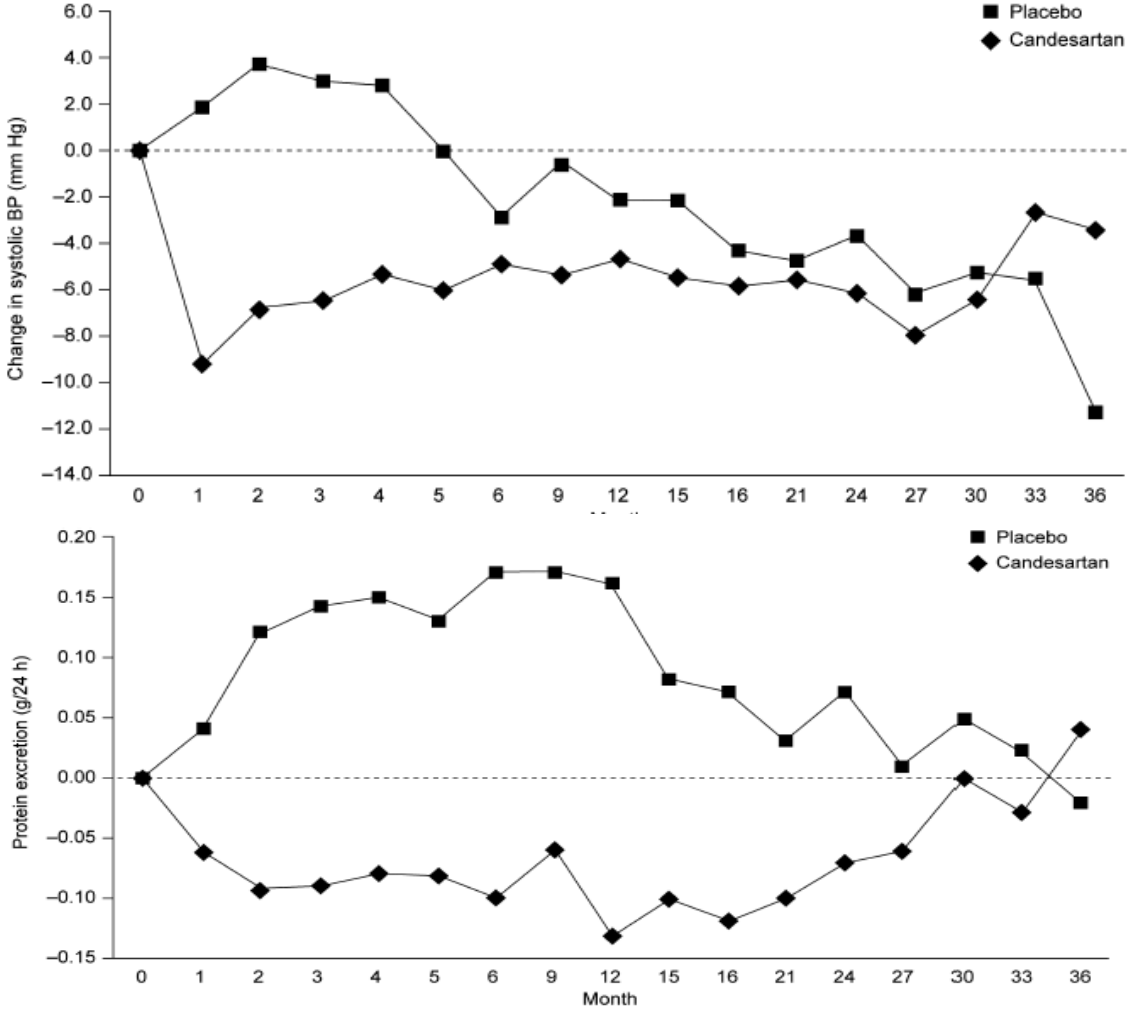
Randomisierte kontrollierte Studien zur RAAS Blockade nach Nierentransplantation

Table 5. Randomized controlled studies of RAAS blockers after renal transplantation.

Study	N	RAAS-blocker	Post-TX (m)	FUP (y)	Δ RR (mmHg)	ΔProteinuria (g/24h)	ΔK^+	Primary endpoint
Paoletti et al.	70	Lisinopril	6	1,5J	NS	NS	NS	**LVH**
Phillip et al.	500	Candesartan	>12	2	**−7/−0.5**	**−0.01/0.03**	NS	Study stopped prematurely
Ibrahim et al.	153	Losartan	2	5	NS	NS	NS	IFTA or ESRD from IFTA
Paoletti et al.	70	Lisinopril	6	10	NS	**0.02/0.4**	NS	**Patient survival/CV morbidity**

Δ RR, ΔProteinuria und ΔK^+ refer to the change (difference) in systolic blood pressure, diastolic blood pressure, proteinuria and serum potassium levels during follow up in the treatment and placebo arm. Statistically significant differences in blood pressure, proteinuria and primary endpoint are shown in bold. Post-Tx: Time after transplantation; FUP: follow-up; ESRD: End stage renal disease; LVH: left ventricular hypertrophy; CV: cardiovascular; IFTA: interstitial fibrosis and tubular atrophy.

Positive Effekte von Candesartan auf Blutdruck und Proteinurie: The SECRET trial



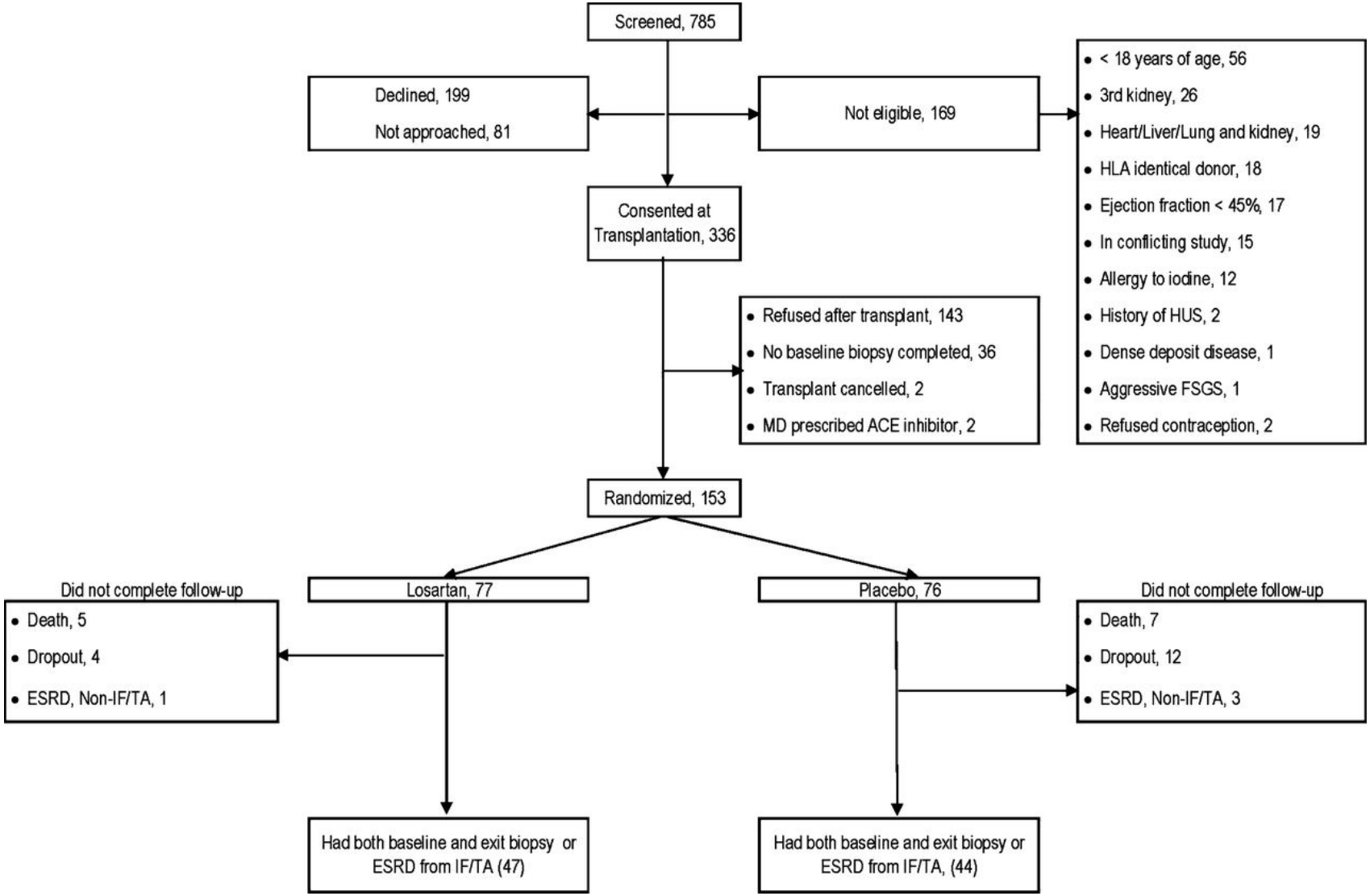
ΔSBD:-6.8 vs. 0.60mmHg
p<0.0001

ΔPR:-0.01 vs. 0.03g/24h
p<0.0001

550 Patienten,
leider vorzeitig abgebrochen

Philipp T et al NDT 2010;25:967-76

Losartan und Nierentransplantation – Studienpatienten



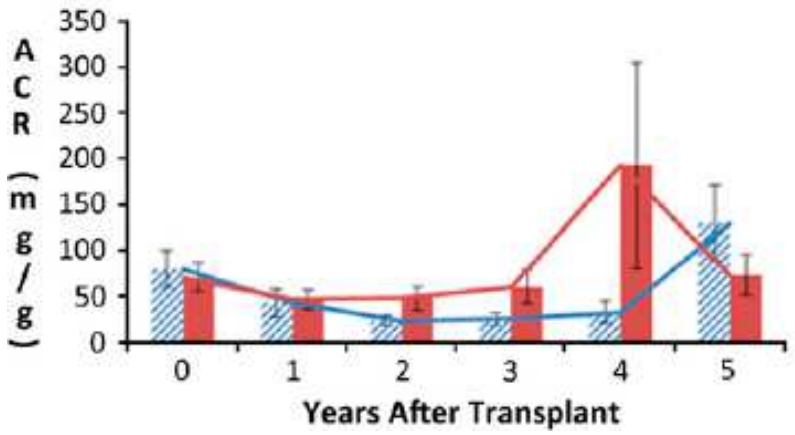
Ibrahim H N et al. JASN 2013;24:320-327

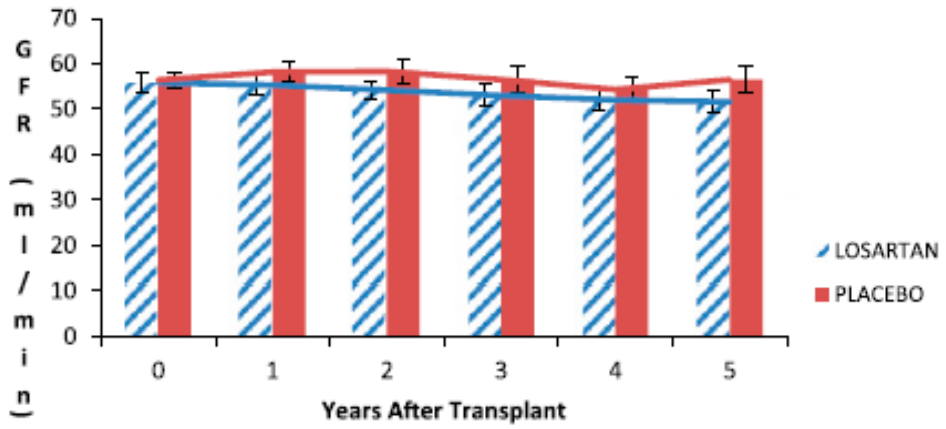
Losartan und Nierentransplantation
- Primäre und sekundäre Endpunkte

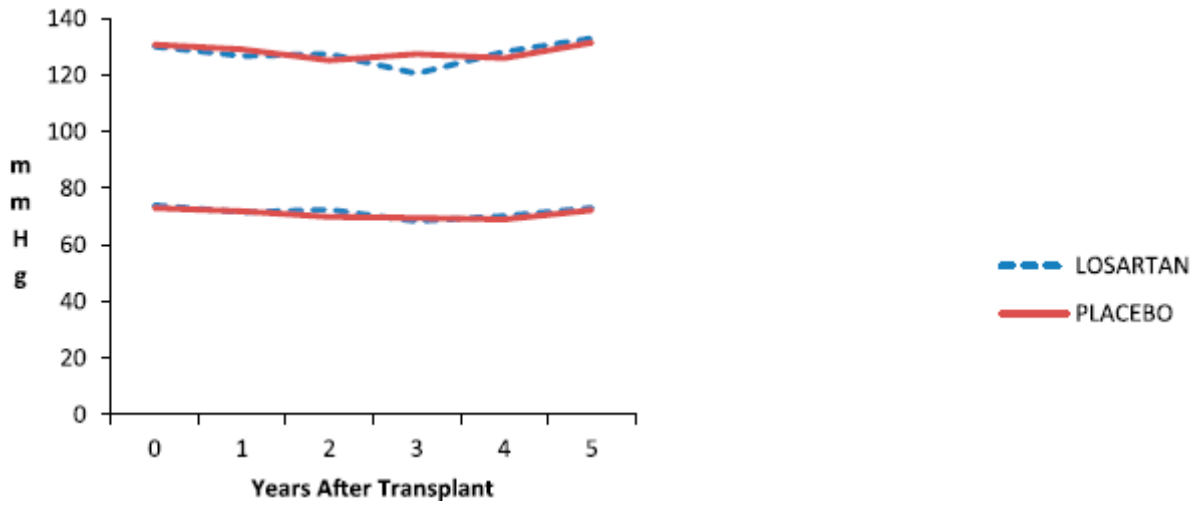
Variable	Losartan Group (*n*=77)	Placebo Group (*n*=76)	OR or HR (95% CI)	*P* Value
Primary endpoint				
Doubling of interstitium or ESRD from IF/TA	6/47	12/44	OR, 0.39 (0.13–1.15)	0.08
Doubling of interstitium	2/47	4/44	OR, 0.44 (0.08–2.56)	0.42
ESRD from IF/TA	4/47	8/44	OR, 0.42 (0.12–1.50)	0.22
Secondary endpoints				
Doubling of interstitium or any ESRD	7/48	15/47	OR, 0.36 (0.13–0.99)	0.05
Doubling of interstitium	2/47	4/44	OR, 0.44 (0.08–2.56)	0.42
All cause ESRD	5/48	11/47	OR, 0.38 (0.12–1.20)	0.09
Time to death any time after randomization	10/77	14/76	HR, 1.38 (0.62–3.20)	0.44
Time to earliest of death, any ESRD, or doubling of creatinine	19/77	24/76	HR, 1.37 (0.75–2.53)	0.30
Doubling of creatinine	9/77	12/76	HR, 7.28 (2.22–32.78)	<0.01
All cause ESRD	4/77	5/76	HR, 0.54 (0.10–2.47)	0.42
Death	6/77	7/76	HR, 0.90 (0.28–3.13)	0.85

Ibrahim H N et al. JASN 2013;24:320-327

Kein Unterschied hinsichtlich der Proteinurie, der Nierenfunktion und der Blutdruckeinstellung

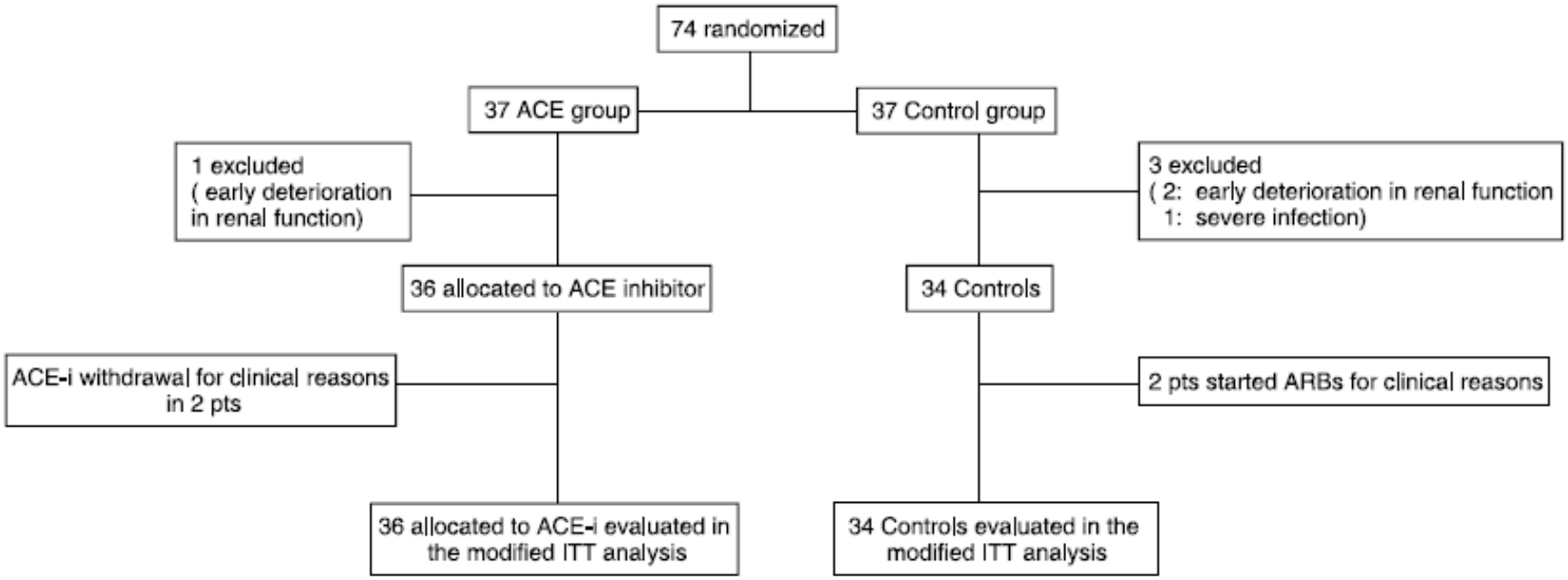






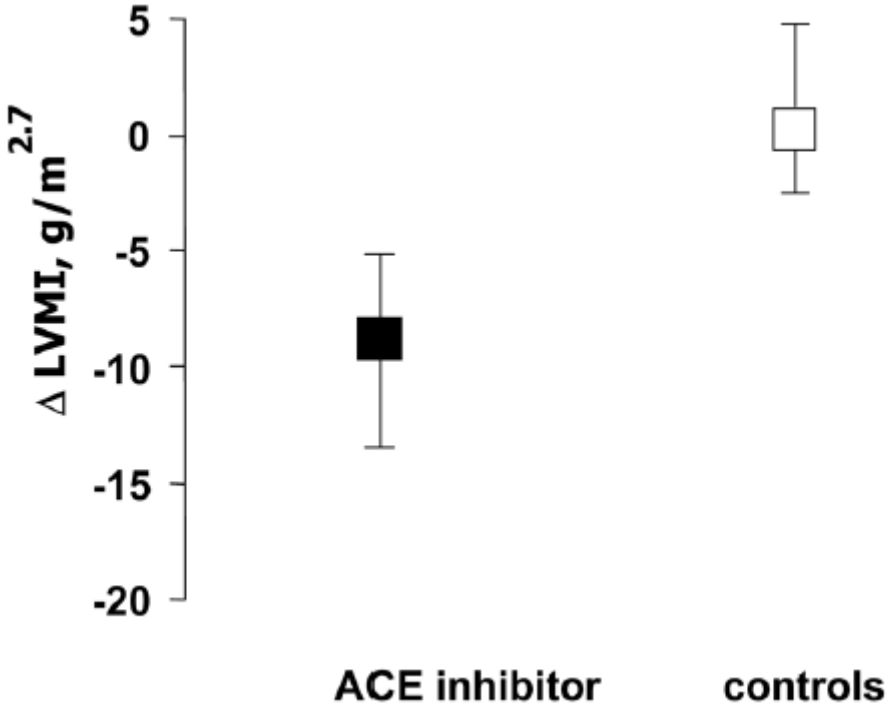
Ibrahim H N et al. JASN 2013;24:320-327

Lisinopril bei nierentransplantierten Patienten mit LVH



Paoletti E et al. AJKD 2007;50:133-142

Regression der LVH in der Lisinopril-Gruppe



P=0.001

Paoletti E et al. AJKD 2007;50:133-142

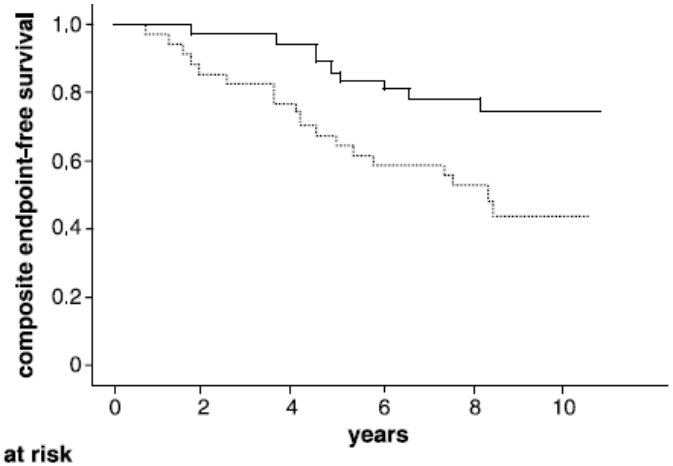
Lisinopril-Studie/Langzeitdaten

	ACE-i (final vs. baseline), mean±SD (*P*)	Controls (final vs. baseline), mean±SD (*P*)	Controls vs. ACE-i, difference (95% CI)	*P*
SBP, mm Hg	132±12	134±12		0.47
Δ SBP, mm Hg	−7±17 (0.023)	−8±19 (0.027)	−0.5±4.5 (−8.5 to 9.6)	0.90
DBP, mm Hg	80±10	82±7		0.46
Δ DBP, mm Hg	−4±13 (0.08)	−3±10 (0.08)	0.7±3.0 (−6.6 to 5.2)	0.81
PP, mm Hg	54±11	52±9		0.42
Δ PP, mm Hg	−0.6±15 (0.81)	−4±14 (0.09)	−3.8±3.6 (−3.3 to 11)	0.29
# Antihypertensives	2.03±0.95	1.90±1.04		0.61
Δ Antihypertensives	0.27±0.91 (0.1)	0.32±1.04 (0.13)	0.05±0.25 (−0.54 to 0.44)	0.84
Patients administered: CCB/b-blockers/diuretics/others	16/15/5/4	21/22/6/10		0.79
Patients administered: CsA/TAC/MMF/S/mTOR inhibitors	16/16/24/27/3	15/14/25/24/2		0.99
s-creatinine, mg/dL	1.73±0.8	1.6±0.67		0.48
Δ s-creatinine, mg/dL	0.25±0.75 (0.066)	0.14±0.60 (0.18)	−0.11±0.17 (−0.23 to 0.45)	0.52
Hgb, g/dL	12.3±1.1	12.6±1.6		0.43
Δ Hgb, g/dL	−0.8±1.4 (0.002)	−0.04±1.9 (0.91)	0.8±0.4 (−1.6 to 0.06)	0.068
Cholesterol, mg/dL	193±33	204±38		0.41
Δ cholesterol, mg/dL	−11±51 (0.08)	−25±62 (0.06)	−14±17 (−20 to 49)	0.41
Triglycerides, mg/dL	140±70	156±89		0.52
Δ Triglycerides, mg/dL	−20±107 (0.4)	−12±123 (0.66)	8±35 (−68 to 62)	0.81
Patients administered ESA/statins/aspirin	15/26/19	12/26/20		0.85
Uric acid, mg/dL	6.3±1.6	6.2±1.4		0.99
Δ Uric acid, mg/dL	−0.04±2.0 (0.91)	−0.36±2.2 (0.43)	−0.3±0.6 (−0.9 to 1.6)	0.61
Urinary protein excretion, g/24 hr	0.39±0.56	0.67±0.68		0.08
Δ Urinary protein excretion, g/24 hr	0.02±0.56 (0.49)	0.39±0.65 (0.021)	0.37±0.15 (−0.07 to 0.68)	0.017

Paoletti E et al. Transplantation 2013; 95:889-895

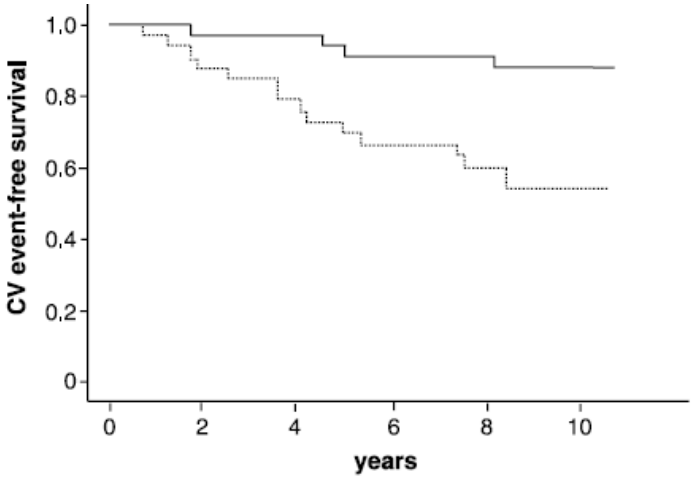
Lisinopril-Studie/Langzeitdaten: Signifikante Effekte auf die kardiovaskuläre Ereignisrate

p=0.0102



No. at risk						
ACE-i	36	35	34	31	30	29
Controls	34	29	26	22	19	18

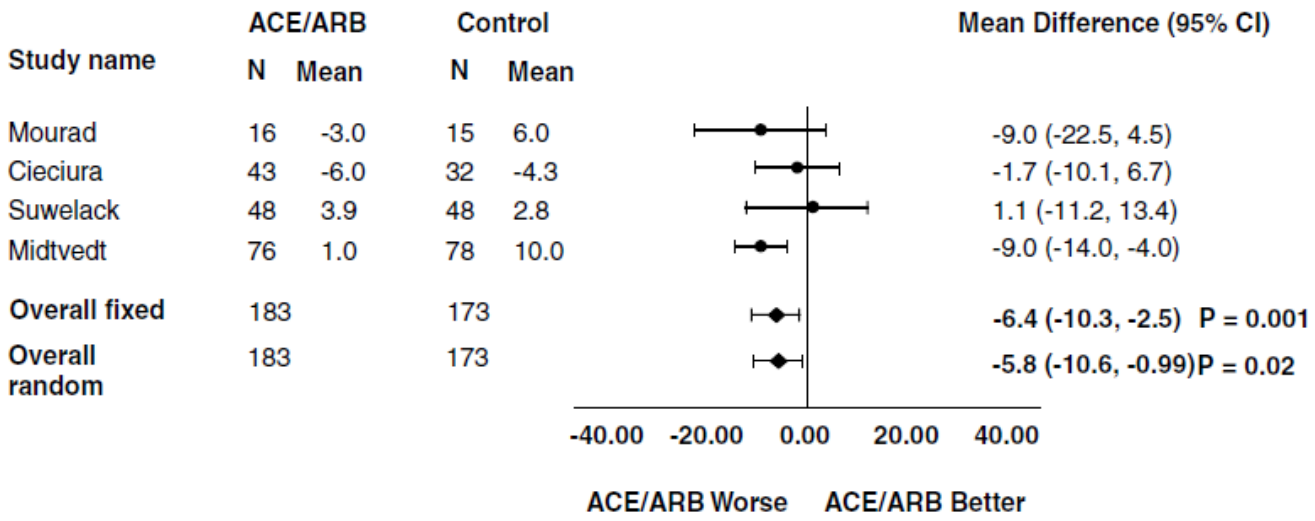
p=0.00027

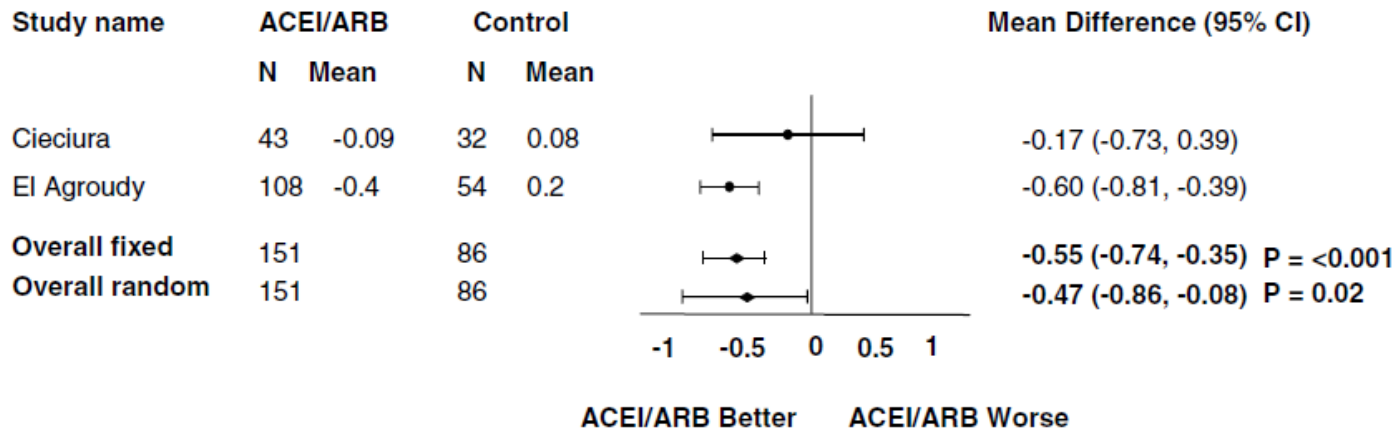


No. at risk						
ACE-i	36	35	35	33	33	32
Controls	34	30	27	23	21	20

Paoletti E et al. Transplantation 2013; 95:889-895

RAAS Blocker nach Nierentransplantation: Effekte auf GFR und Proteinurie

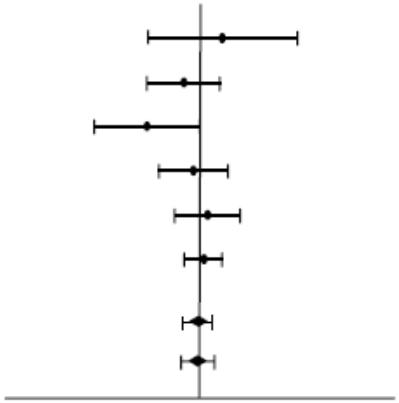




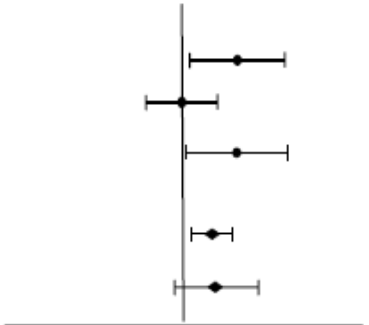
Hiremath S, AJT 2007;7:2350-60

RAAS Blocker nach Nierentransplantation: Effekte auf Blutdruck und Kalium

Study name	ACEI/ARB N	ACEI/ARB Mean	Control N	Control Mean	Mean Difference (95% CI)
Mourad	16	-10	15	-13	3.0 (-7.2, 13.2)
Cieciura	43	-2	32	-0.5	-2.3 (-7.3, 2.7)
Hernandez D	29	-5	32	1.6	-7.4 (-14.8, -0.02)
Suwelack	48	-6	48	-5	-1.0 (-5.7, 3.7)
Takahara	41	-7	78	-8	1.0 (-3.5, 5.5)
El Agroudy	108	-12	78	-13	0.5 (-2.1, 3.1)
Overall fixed	285		212		**-0.37 (-2.2, 1.4) P = 0.68**
Overall random	285		212		**-0.45 (-2.4, 1.5) P = 0.65**



Study name	ACE/ARB N	ACE/ARB Mean	Control N	Control Mean	Mean Difference (95% CI)
Mourad	16	0.00	15	-0.30	0.3 (0.05, 0.55)
El Agroudy	108	0.20	54	0.20	0 (-0.19, 0.19)
Formica	29	-0.30	27	-0.60	0.3 (0.04, 0.56)
Overall fixed	124		69		**0.16 (0.03, 0.28) P = 0.02**
Overall random	124		69		**0.18 (-0.03, 0.40) P = 0.09**

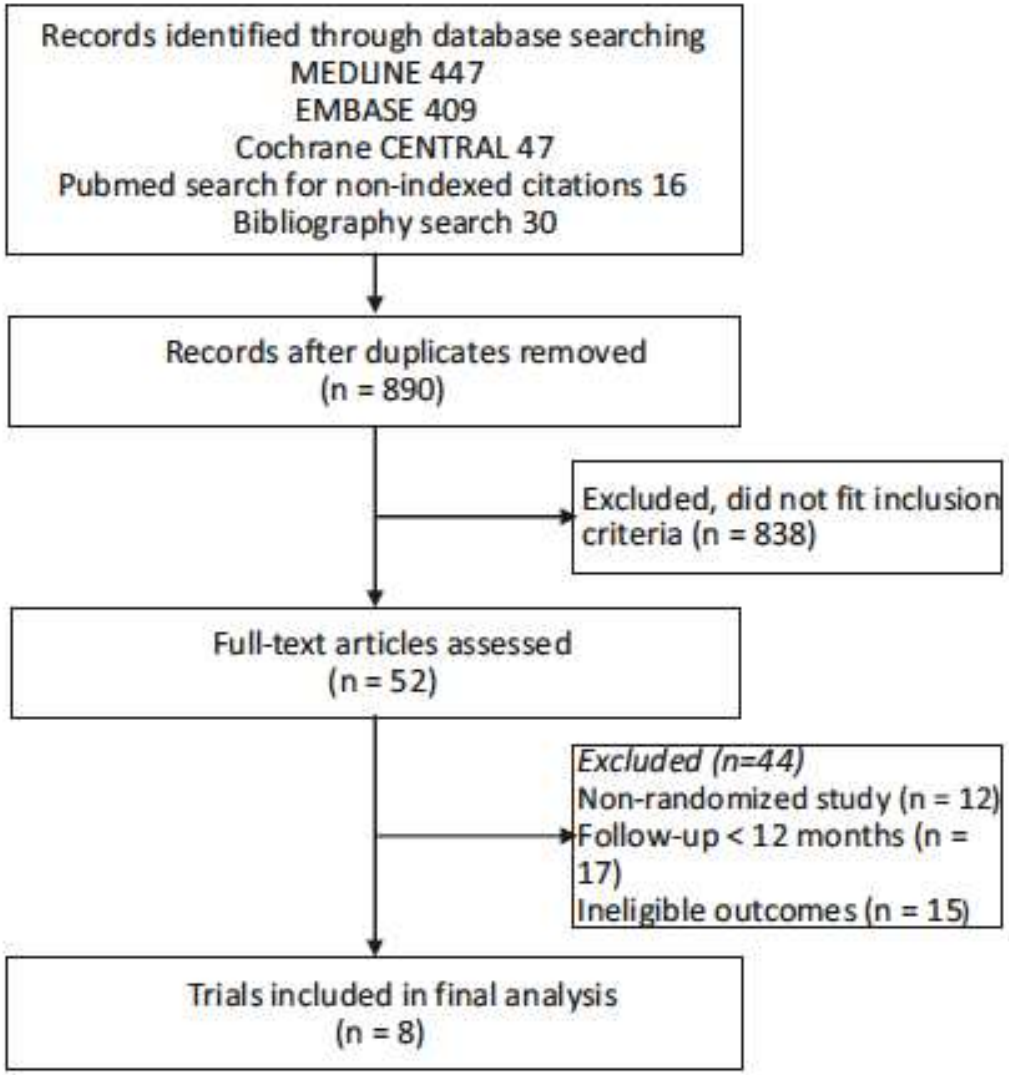


-0.80 -0.40 0.00 0.40 0.80

ACE/ARB Better ACE/ARB Worse

Hiremath S, AJT 2007;7:2350-60

RAAS Blockade und Nierentransplantation – aktuellste Metaanalyse (8 Studien, 1502 Patienten)



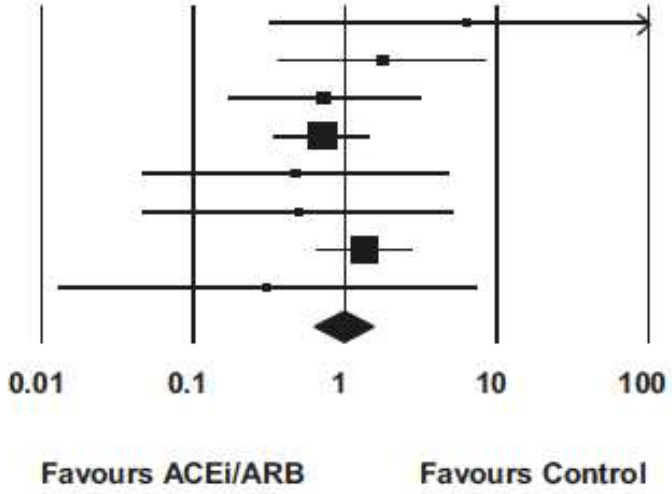
Hiremath S und Knoll G AJKD 2016 online

RAAS Blockade und Nierentransplantation – aktuellste Metaanalyse (8 Studien, 1502 Patienten)

Mortalität

Trial	Year	Risk ratio	95% CI		p	Dead / Total RAS blockade	Dead / Total Control	Relative weight
Midtvedt	2001	6.36	0.31	129.85	0.2	2 / 54	0 / 69	2.19
Amara	2010	1.76	0.36	8.70	0.5	4 / 25	2 / 22	7.81
Philipp	2010	0.73	0.16	3.21	0.7	3 / 255	4 / 247	9.02
Ibrahim	2013	0.71	0.33	1.49	0.4	10 / 77	14 / 76	35.72
Paoletti	2013	0.47	0.04	4.97	0.5	1 / 36	2 / 34	3.60
Salzberg	2014	0.49	0.05	5.30	0.6	1 / 66	2 / 65	3.53
Knoll	2015	1.35	0.64	2.83	0.4	14 / 103	11 / 109	36.17
Mandelbrot	2015	0.30	0.01	7.41	0.5	0 / 138	1 / 126	1.96
Summary RR		**0.96**	**0.62**	**1.51**	**0.9**			

Q 4.8; p 0.87; $I^2 = 0\%$



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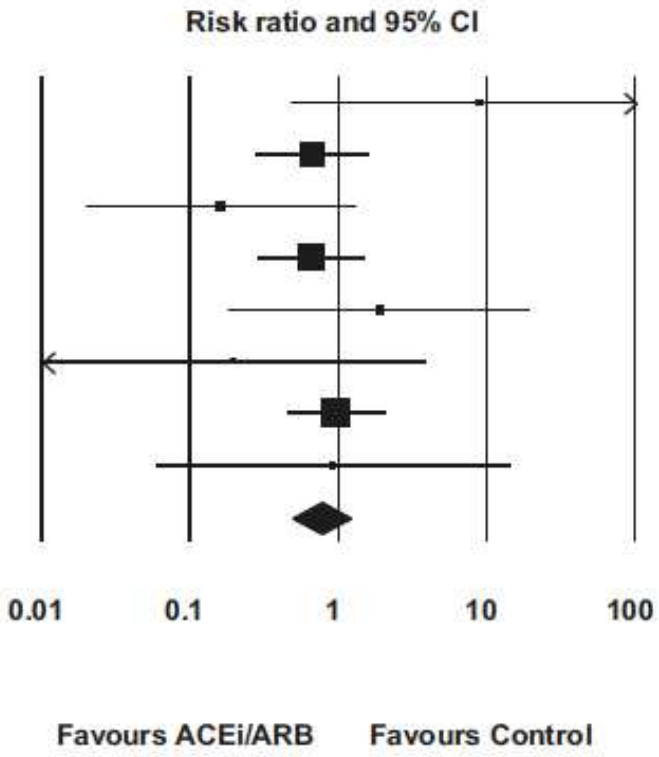
RAAS Blockade und Nierentransplantation – aktuellste Metaanalyse (8 Studien, 1502 Patienten)

Verdoppelung des Serumkreatinins

Trial	Year	Risk ratio	95% CI		p	Graft failure / Total: RAS blockade	Graft failure / Total: Control	Relative weight
Midtvedt	2001	8.91	0.47	168.87	0.2	3 / 54	0 / 69	2.25
Amara	2010	0.66	0.27	1.61	0.4	6 / 25	8 / 22	24.62
Philipp	2010	0.16	0.02	1.33	0.09	1 / 255	6 / 247	4.38
Ibrahim	2013	0.66	0.29	1.52	0.3	8 / 77	12 / 76	27.86
Paoletti	2013	1.89	0.18	19.89	0.6	2 / 36	1 / 34	3.52
Salzberg	2014	0.20	0.01	4.03	0.3	0 / 66	2 / 65	2.14
Knoll	2015	0.97	0.45	2.10	0.9	11 / 103	12 / 109	32.67
Mandelbrot	2015	0.91	0.06	14.44	0.9	1 / 138	1 / 126	2.56
Summary RR		**0.76**	**0.49**	**1.18**	**0.2**			

Q 6.7; p 0.46 $I^2 = 0\%$



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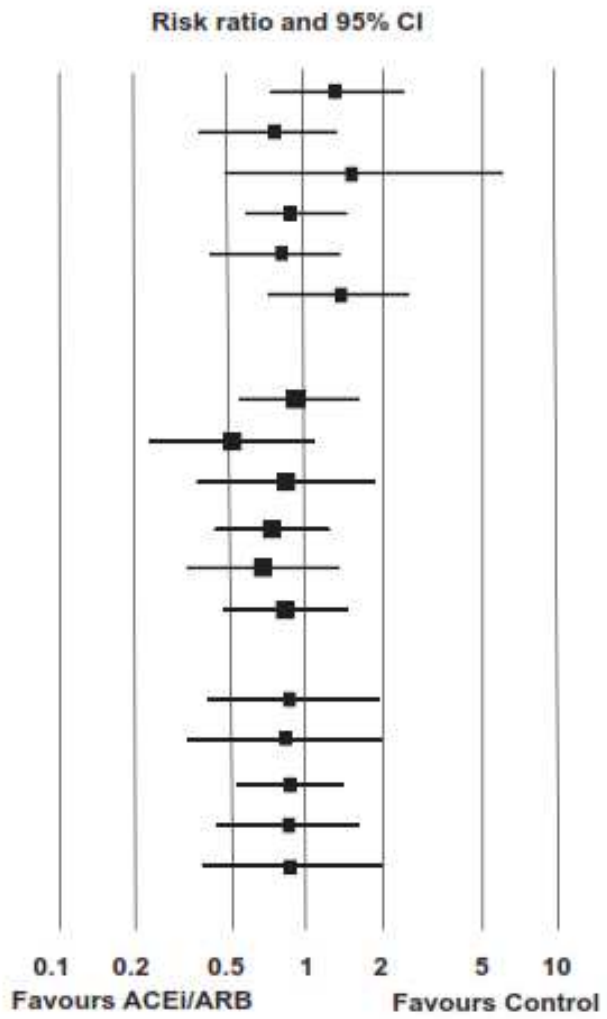
RAAS Blockade und Nierentransplantation – aktuellste Metaanalyse (8 Studien, 1502 Patienten)

	Risk ratio	Lower limit	Upper limit	p-Value
All cause mortality				
ACEi vs control	1.32	0.71	2.45	0.4
ARB vs control	0.69	0.36	1.31	0.3
Follow up 1 year	1.67	0.46	6.08	0.4
Follow up > 1 year	0.89	0.56	1.44	0.7
Proteinuria not an inclusion criteria	0.74	0.40	1.35	0.3
Proteinuria was an inclusion criteria	1.32	0.68	2.56	0.4
Graft Failure				
ACEi vs control	0.94	0.54	1.64	0.8
ARB vs control	0.51	0.24	1.09	0.08
Follow up 1 year	0.83	0.36	1.91	0.7
Follow up > 1 year	0.73	0.43	1.25	0.3
Proteinuria not an inclusion criteria	0.67	0.33	1.36	0.3
Proteinuria was an inclusion criteria	0.83	0.46	1.48	0.5
Doubling of creatinine				
ACEi vs control	0.87	0.39	1.94	0.7
ARB vs control	0.80	0.33	1.97	0.6
Follow up > 1 year*	0.84	0.51	1.39	0.5
Proteinuria not an inclusion criteria	0.83	0.43	1.61	0.6
Proteinuria was an inclusion criteria	0.87	0.37	2.00	0.7



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RAASB in der frühen postoperativen Phase nach Nierentransplantation

Group I

142 CASES
(received a RAASB at day 8 for BP control)

6w Bx in 96pts

12w Bx in 89 pts

6+12w Bx in 72 pts

17 pts discontinued the RAASB at week 11 post-Tx

8 pts lost to follow-up

117 patients were treated with a RAASB in the first year

114 CONTROLS
(matched according to sex, year of transplantation and creatinine at day 8)

6w Bx in 83 pts

12w Bx in 78 pts

6+12w Bx in 70 pts

RAASB was added in 59 pts at week 18 post-Tx

6 pts lost to follow-up

Group II

50 patients were treated without a RAASB in the first year

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RAASB in der frühen postoperativen Phase nach Nierentransplantation

Table 1. Baseline demographic and clinical characteristics in group I and group II.

	Group I			Group II		
	RAASB	No RAASB	*p* Value	RAASB	No RAASB	*p* Value
Patients (*n*)	142	114		117	50	
Age at transplantation (yrs)	46.9 ± 13.7	48.1 ± 13.9	0.47	46.4 ± 14.2	47.1 ± 14.0	0.78
Male gender, *n* (%)	78 (54.9)	63 (55.3)	0.96	65 (55.6)	23 (46.0)	0.26
Years on dialysis	4.4 ± 3.0	4.8 ± 3.1	0.23	4.2 ± 2.9	5.2 ± 3.0	**0.06**
History of CVD, *n* (%)	22 (15.5)	22 (19.3)	0.42	20 (17.1)	7 (14.0)	0.62
Diabetes mellitus	18 (12.7)	19 (16.7)	0.37	15 (12.8)	6 (12.0)	0.88
Re-transplantation, *n* (%)	11 (7.7)	18 (15.8)	**0.04**	9 (7.7)	9 (18.0)	**0.05**
Living donor, *n* (%)	66 (46.5)	40 (35.4)	**0.07**	59 (50.4)	15 (30.6)	**0.02**
Mismatches			0.10			0.32
0–2, *n* (%)	49 (37.2)	49 (47.6)		38 (34.9)	21 (45.6)	
2–4, *n* (%)	61 (46.2)	37 (35.9)		51 (46.8)	17 (36.9)	
4–6, *n* (%)	22 (16.6)	17 (16.5)		20 (18.4)	8 (17.3)	
Cold ischemia time (hrs), median [range]	7.9 [1.3–26.8]	10.1 [1.5–32.8]	0.27	6.3 [1.3–26.8]	11.1 [1.5–23.0]	**0.08**
Delayed graft function, *n* (%)	5 (3.6)	4 (3.6)	0.98	4 (3.5)	3 (6.1)	0.44

Bold values denote statistically significant differences ($p < 0.05$).

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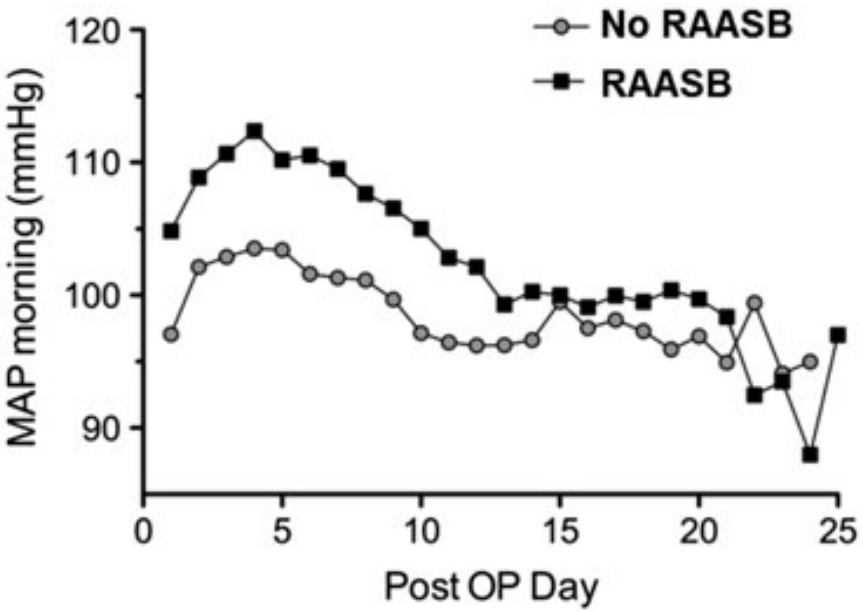
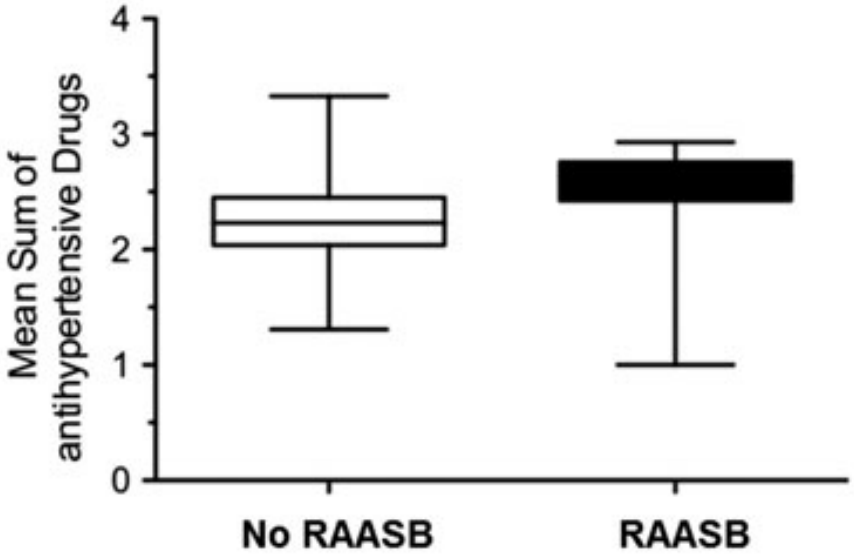
RAASB in der frühen postoperativen Phase nach Nierentransplantation





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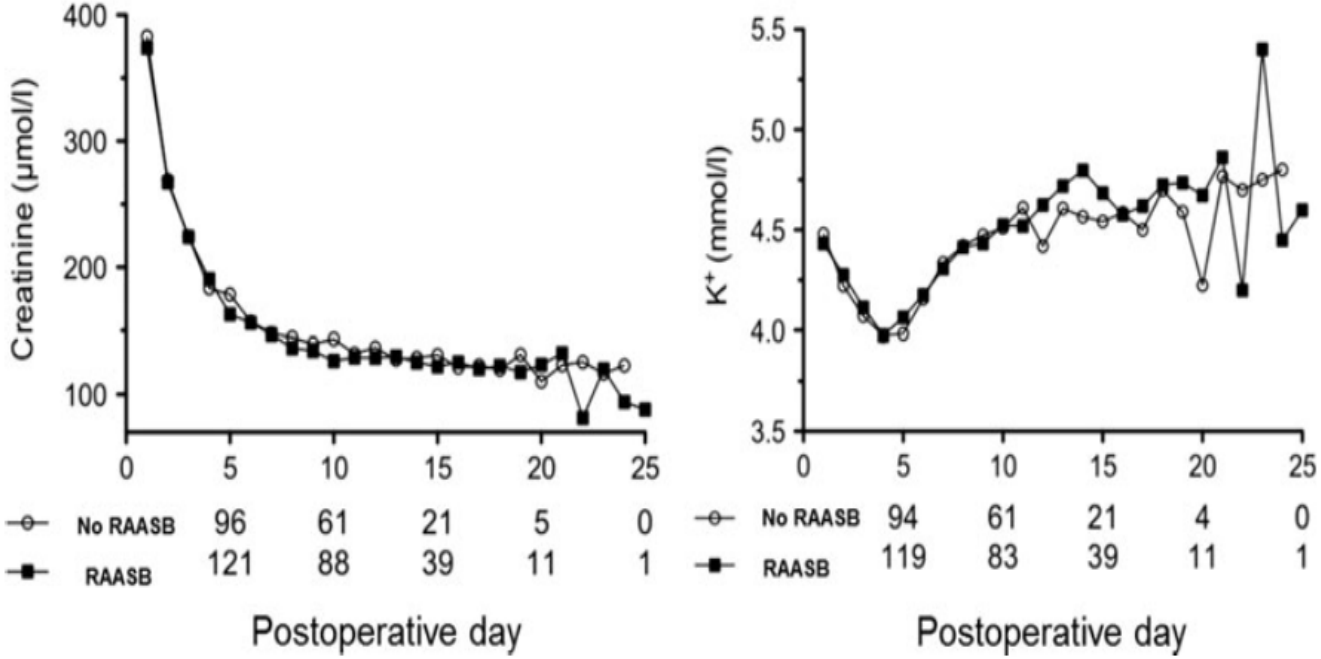
RAASB in der frühen postoperativen Phase nach Nierentransplantation

Kein Unterschied hinsichtlich der Nierenfunktion und des Serumkaliums



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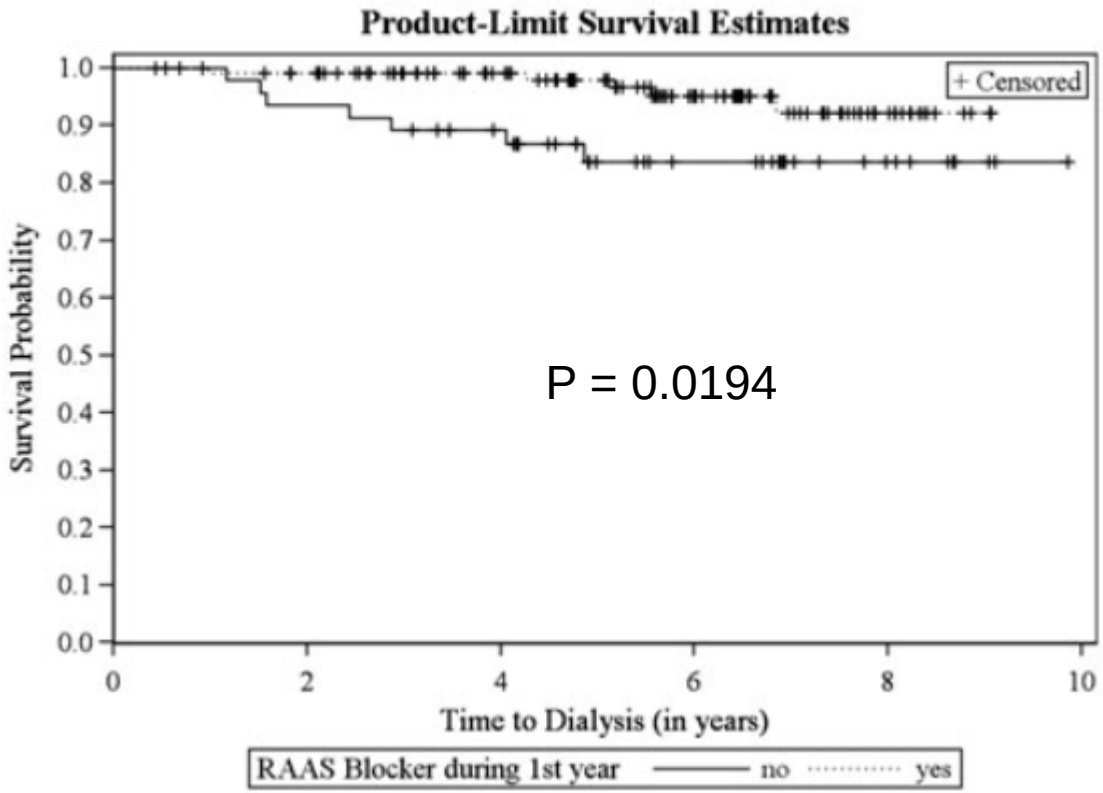
RAASB in der frühen postoperativen Phase nach Nierentransplantation



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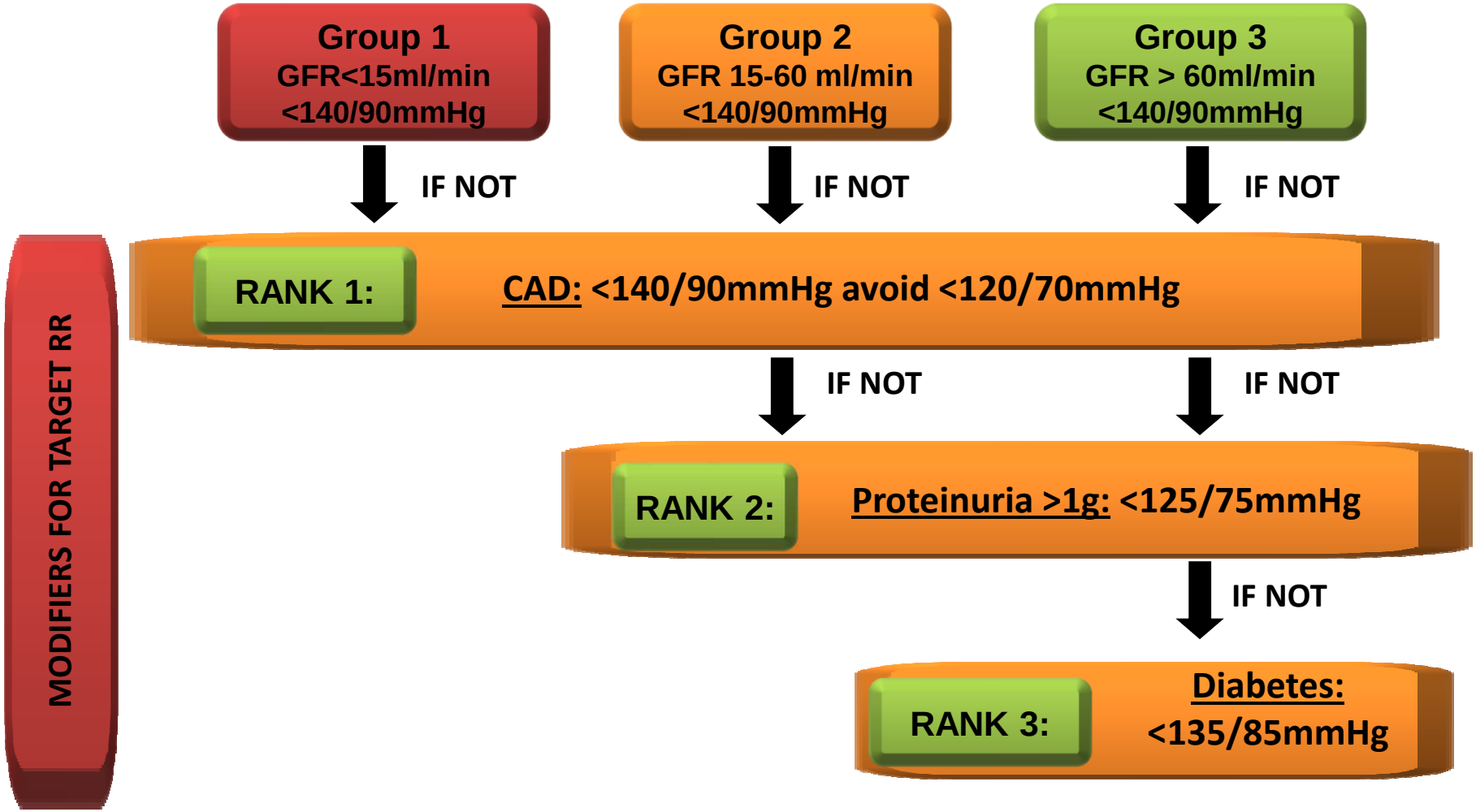
Zusammenfassung

- Die Anzahl der randomisert kontrollierten Hypertoniestudien nach Nierentransplantation ist sehr gering
- In einzelnen Studien hat RAAS-Blockade eine positive Wirkung auf das Patientenüberleben und das Transplantat
- Eine allgemeine Empfehlung über Vorteile der RAAS Blockade in Bezug auf das Transplantat- und Patientenüberleben ist anhand der Meta-Analysen nicht möglich
- Eine individualisierte antihypertensive Therapie-Strategie ist notwendig
- ACEIs/ARBs sind sichere und effektive Antihypertensiva unmittelbar nach Nierentransplantation

Arterielle Hypertonie nach Nierentransplantation



Chatzikyrkou et al J Hypertens 2011;29 (12):2283-94

Affiliation and Disclosures

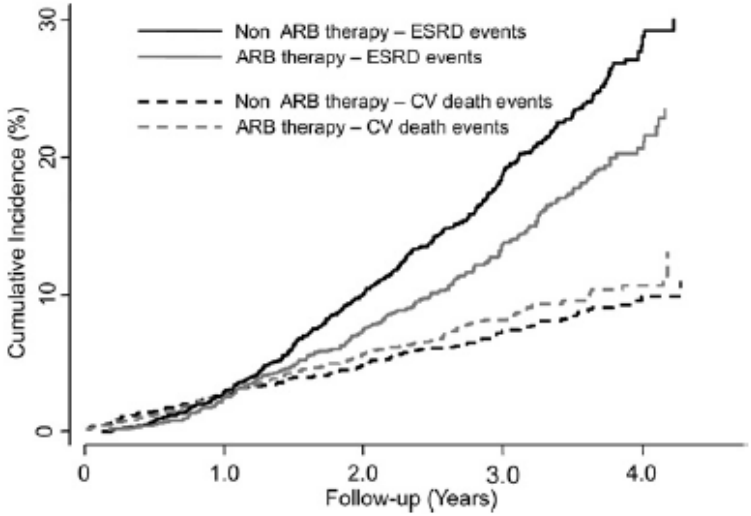
- Alexion, Bayer, Noxxon, Astra-Zeneca, Fresenius, CVRx, Vifor, Fresenius, phenos GmbH: Consultancy and lecture fees, travel grants
- Novartis, Daiichi-Sankyo, BMS, Boehringer: Lecture fees

Medizinische Hochschule Hannover

RAASB in der sehr frühen postoperativen Phase nach Nierentransplantation

Post-Operative Day	1			8			13			21		
	No ACE	**ACE**	***p***	**No ACE**	**ACE**	***p***	**No ACE**	**ACE**	***p***	**No ACE**	**ACE**	***p***
Potassium (mmol/l)	4.48 ± 0.52	4.43 ± 0.48	*0.61*	4.42 ± 0.59	4.41 ± 055	*0.93*	4.61 ± 0.62	4.73 ± 0.61	*0.33*	4.77 ± 0.25	4.85 ± 0.48	*0.77*
Creatinine (µmol/l)	383 ± 201	374 ± 220	*0.75*	145 ± 58	136 ± 60	*0.36*	127 ± 39	129 ± 38	*0.84*	123 ± 11	133 ± 43	*0.71*
eGFR (ml/min)	20 ± 16	23 ± 19	*0.34*	41 ± 21	56 ± 19	*06*	58 ± 22	55 ± 17	*0.50*	61 ± 8	53 ± 12	*0.33*
Morning RR systolic	137 ± 20	147 ± 19	***0.002***	141± 16	150 ± 17	***<0.001***	134 ± 15	137 ± 16	*0.23*	130 ± 19	138 ± 21	*0.49*
Morning RR diastolic	77 ± 12	84 ± 12	***<0.001***	81 ± 11	86 ± 12	***0.001***	77 ± 11	80 ± 10	*0.12*	77 ± 12	79 ± 10	*0.82*
Morning MAP	97 ± 13	105 ± 13	***<0.001***	101 ± 11	108 ± 11	***<0.001***	96 ± 11	99 ± 11	*0.11*	95 ± 14	98 ± 12	*0.62*

Renal events versus cardiovascular death in RENAAL(n=1513) and IDTN(n=1590)



	Renal events	CV events
	/100pt-y	/100pt-y
UACR		
<1g/g	1.9	2.5
1.0-2.0g/g	4.6	2.3
>2g/g	16.0	4.0
eGFR		
>45ml/min/1.73m^2	1.8	2.9
30-45 ml/min/1.73m^2	6.9	2.5
<30 ml/min/1.73m^2	21.2	3.8

Packham D, Am J Kidney Dis 2012; 59:75-83

Renoprotektive Effekte von Losartan nach Nierentransplantation

Table 2: Influence of therapy on the ambulatory blood pressure, renal function, urine NAG, α1m, TGF-β1, PIIINP and cyclosporine level

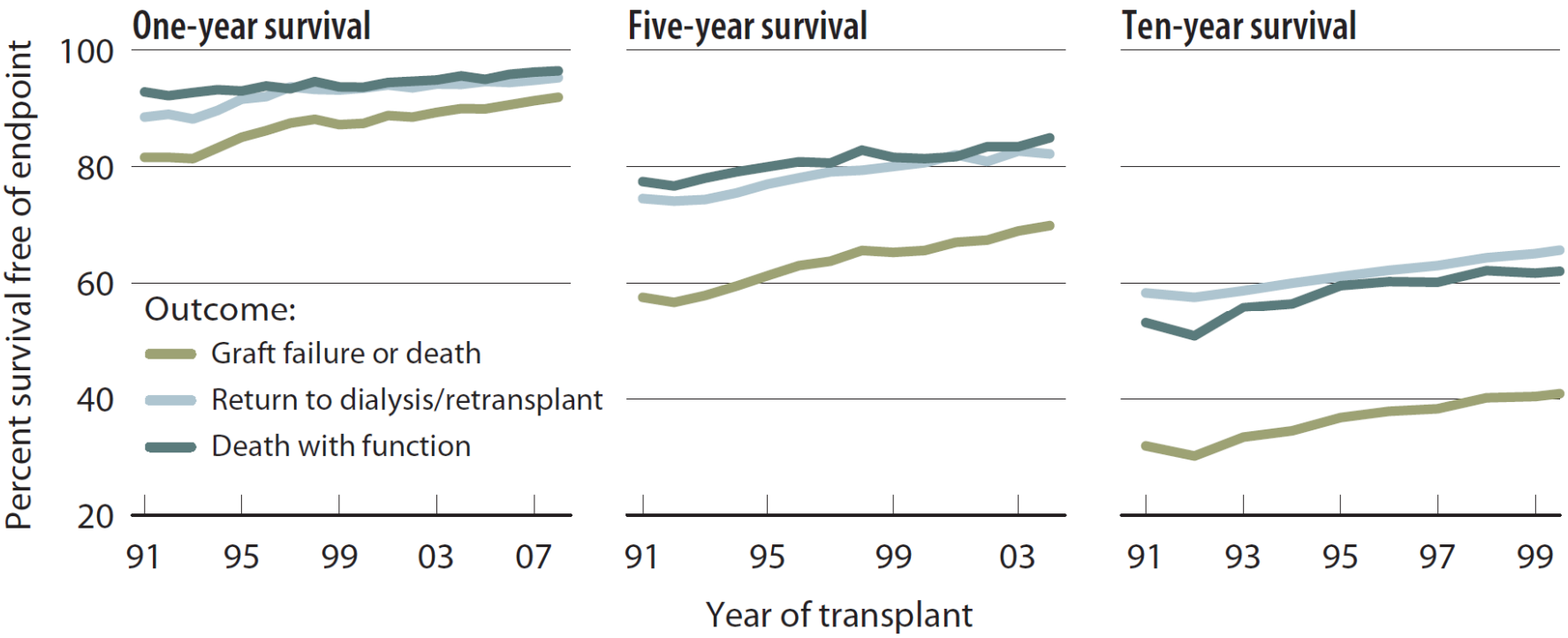
	Losartan	Placebo	Carvedilol	P
SBP (mmHg)	118.6 ± 2.7	120.4 ± 2.6	118.7 ± 2.0	NS
DBP (mmHg)	73.7 ± 1.8	76.7 ± 1.2	75.9 ± 1.3	NS
Day SBP (mmHg)	119.1 ± 2.7	121.3 ± 2.4	120.6 ± 1.8	NS
Day DBP (mmHg)	74.7 ± 2.0	76.7 ± 1.0	76.8 ± 1.1	NS
Night SBP (mmHg)	109.3 ± 3.7	115.3 ± 3.9	112.7 ± 2.5	NS
Night DBP (mmHg)	67.3 ± 2.2	70.7 ± 1.9	70.4 ± 1.3	NS
Creatinine (mg/dL)	1.37 ± 0.04	1.34 ± 0.05	1.38 ± 0.06	NS
Creatinine clearance (mL/min)	60.76 ± 3.10	61.84 ± 3.09	60.04 ± 2.69	NS
Cyclosporine (ng/mL)	163.5 ± 13.44	176.1 ± 10.73	169.8 ± 13.54	NS
NAG iu/g creatinine	3.24 ± 0.56[1,2]	6.18 ± 1.24	4.61 ± 0.8	ANOVA ($p < 0.05$)
Alfa-1 microglobulin mg/g creatinine	4.3 ± 1.92[1,2]	12.98 ± 3.38	8.88 ± 4.02	ANOVA ($p < 0.05$)
TGF-β1 pg/mg creatinine	16.43 ± 2.18[1,2]	27.91 ± 18.33	28.8 ± 14.36	ANOVA ($p < 0.05$)
PIIINP mcg/g creatinine	2.45 ± 0.3[1]	4.7 ± 1.28	3.07 ± 0.51	ANOVA ($p < 0.05$)

SBP = systolic blood pressure; DBP = diastolic blood pressure; NAG = N-acetyl-β-D-glucosaminidase; TGF-β1 = transforming growth factor β1; PIIINP = amino-terminal propeptide of type III procollagen.
[1]Significant relative to placebo (*post hoc*: $p < 0.05$).
[2]Significant relative to carvedilol (*post hoc*: $p < 0.05$).

- **17 Patienten**
- **2 x 3 cross over design**
- **6,5J post-TX**
- **Dauer 8 Wochen**

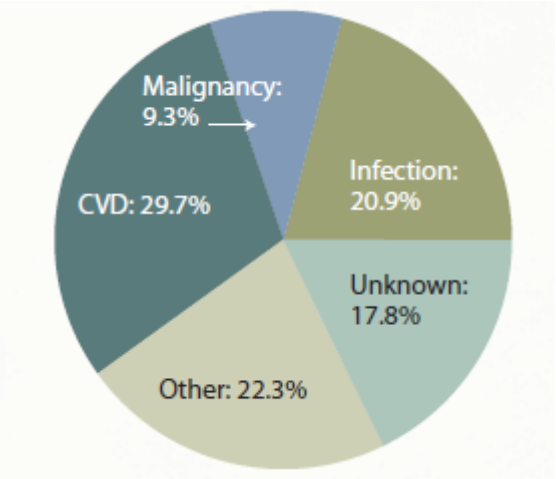
Tylicki L et al AJT 2007; 7:243-48

Langzeitüberleben der Nierentransplantate hat sich nicht wesentlich gebessert

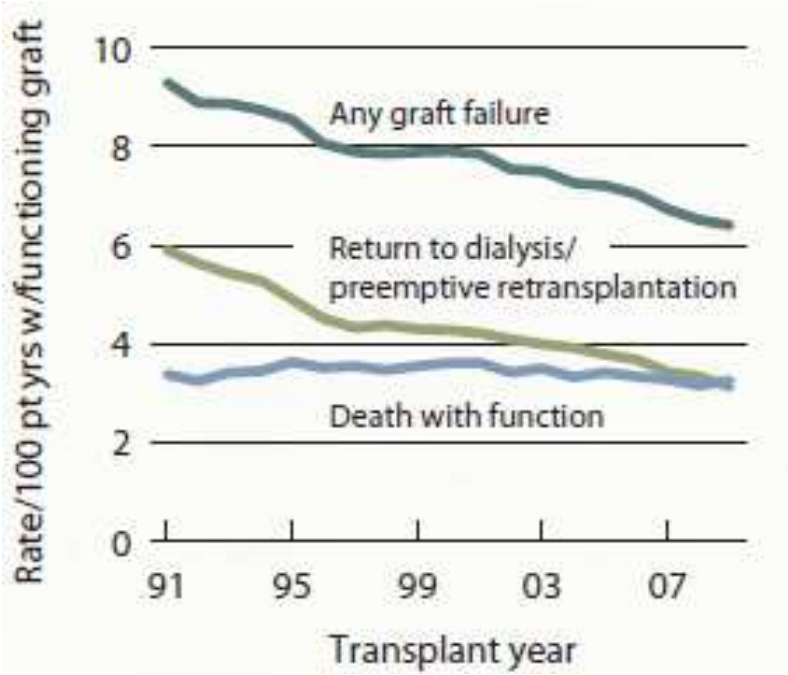


US Renal Data 2011 Annual Report

Todesursachen von Patienten mit funktionierendem Transplantat



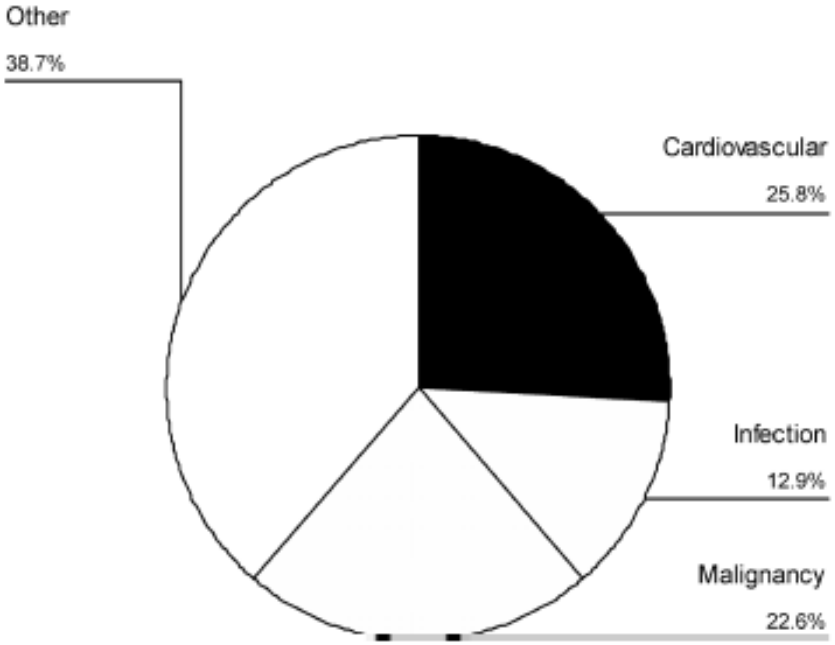
Ergebnisse nach Nierentransplantation



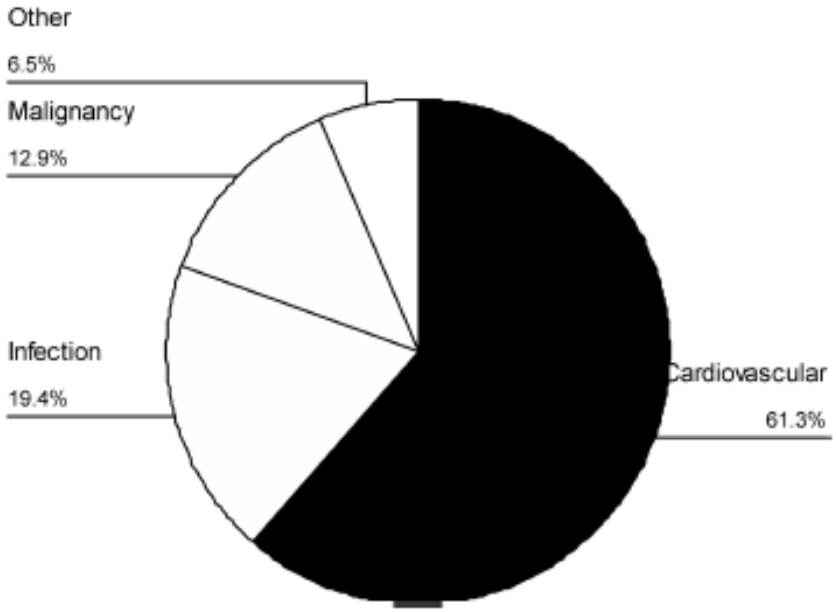
US Renal Data 2011 Annual Report

Todesursachen transplantierter Patienten mit und ohne Diabetes mellitus

Nicht-Diabetiker



Diabetiker



Cosio et al AJT 2008; 8:593-599

RCT Studien in Nierentransplantation: Ein Mangel an ausreichenden Patientenzahlen (α=0.05, power=80%, 10% loss to FUP, SD 20ml/min)

	Difference in [1]GFR between two independent groups		
[1]Standard deviation	5	7.5	10
15	318	142	82
20	562	251	142
25	876	391	222

[1]in mL/min.

	Difference in [1]GFR between two independent groups		
[1]Standard deviation	5	7.5	10
15	11	36	55
20	7	23	36
25	2	9	25

[1]in mL/min.

Ibrahim et al AJT 2013; 13:707-713