Das nephrologische Jahr 2013/2014
Neues, aktuelle Studien und Highlights

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CKD-Stadium und Überweisung zum Nephrologen

KDIGO-Leitlinien 2013
www.kdigo.org

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90		Monitor	Refer*
	G2	Mildly decreased	60–89		Monitor	Refer*
	G3a	Mildly to moderately decreased	45–59	Monitor	Monitor	Refer
	G3b	Moderately to severely decreased	30–44	Monitor	Monitor	Refer
	G4	Severely decreased	15–29	Refer*	Refer*	Refer
	G5	Kidney failure	<15	Refer	Refer	Refer

N Engl J Med, 18. Nov. 2013

ORIGINAL ARTICLE

Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis

Christopher J. Cooper, M.D., Timothy P. Murphy, M.D., Donald E. Cutlip, M.D., Kenneth Jamerson, M.D., William Henrich, M.D., Diane M. Reid, M.D., David J. Cohen, M.D., Alan H. Matsumoto, M.D., Michael Steffes, M.D., Michael R. Jaff, D.O., Martin R. Prince, M.D., Ph.D., Eldrin F. Lewis, M.D., Katherine R. Tuttle, M.D., Joseph I. Shapiro, M.D., M.P.H., John H. Rundback, M.D., Joseph M. Massaro, Ph.D., Ralph B. D'Agostino, Sr., Ph.D., and Lance D. Dworkin, M.D., for the CORAL Investigators*

Limitation: **Studie „…open to patients whose doctors were in a state of equipoise about the role of renal-artery stenting for stenoses of only 60%"**

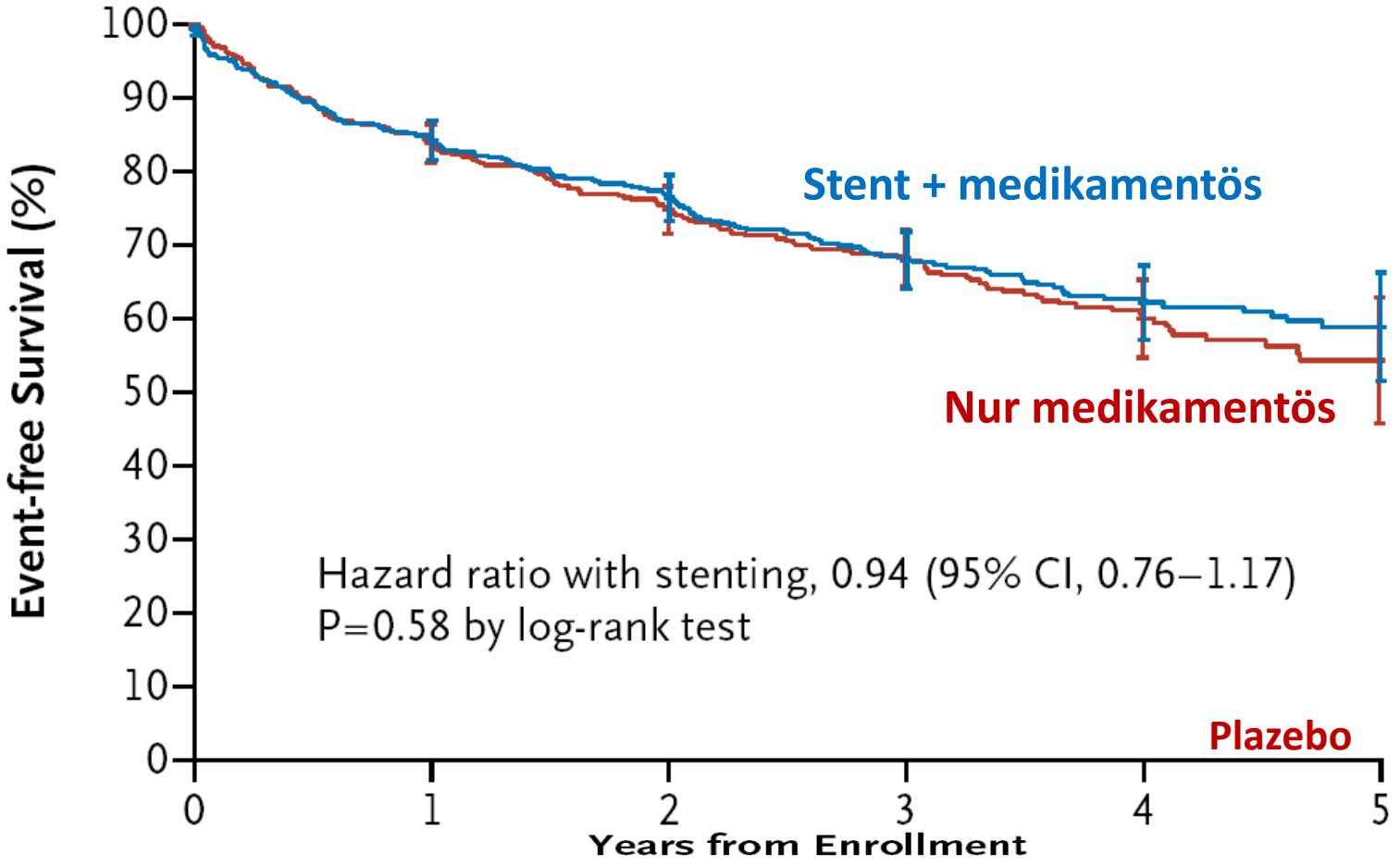
Stärke: **"…Severe renal-artery stenosis defined angiographically as > 80% or >60% but <80%**, with a systolic pressure gradient of at least 20 mm Hg**…."**

Nieren-arterien-stenose

Cooper CJ et al, N Engl J Med 2013, 18. Nov

CORAL: Stent vs. medik. Therapie der atherosklerotischen Nierenarterienstenose

Primärer Kombi-Endpunkt: Kardiovask. Tod, Infarkt, Apoplex, Herzinsuff. Hospitalisierung, CKD Progress, ESRD



No. at Risk						
Medical therapy alone	472	371	314	214	115	40
Stent plus medical therapy	459	362	318	224	131	59

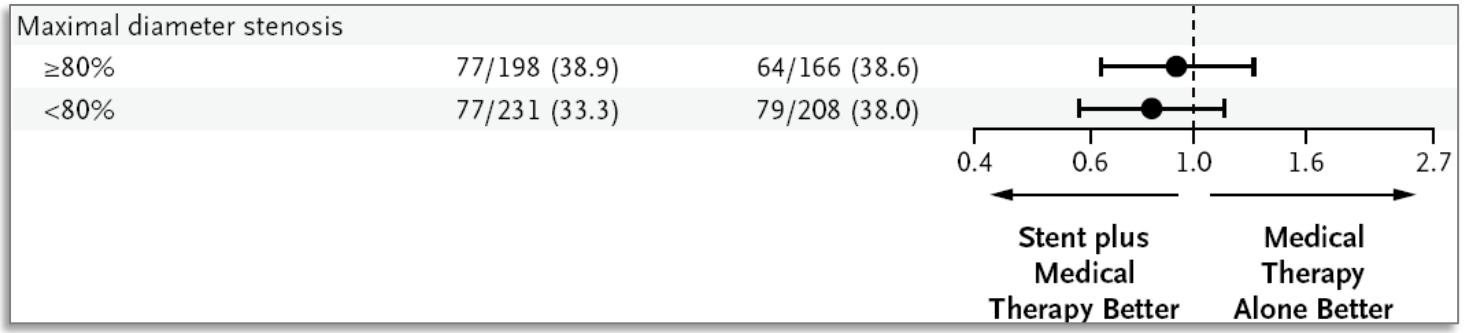
Cooper CJ et al, N Engl J Med 2013, 18. Nov

CORAL: Stent vs. medik. Therapie der atherosklerotischen Nierenarterienstenose

Society for Cardiovascular Angiography and Interventions (SCAI)

For patients who fail medical therapy or are unable to tolerate medical therapy, stenting remains a reasonable option, SCAI stated.

- CORAL findings also showed that the benefit of medical therapy alone lessened over time.
- Worthy of continued study… is the treatment of patients with hemodynamically severe lesions and those who fail medical therapy.
- Similar to other patient populations, in the real-world setting, optimal medical therapy may present challenges with respect to compliance and tolerance of medications.



N Engl J Med 9.November 2013

ORIGINAL ARTICLE

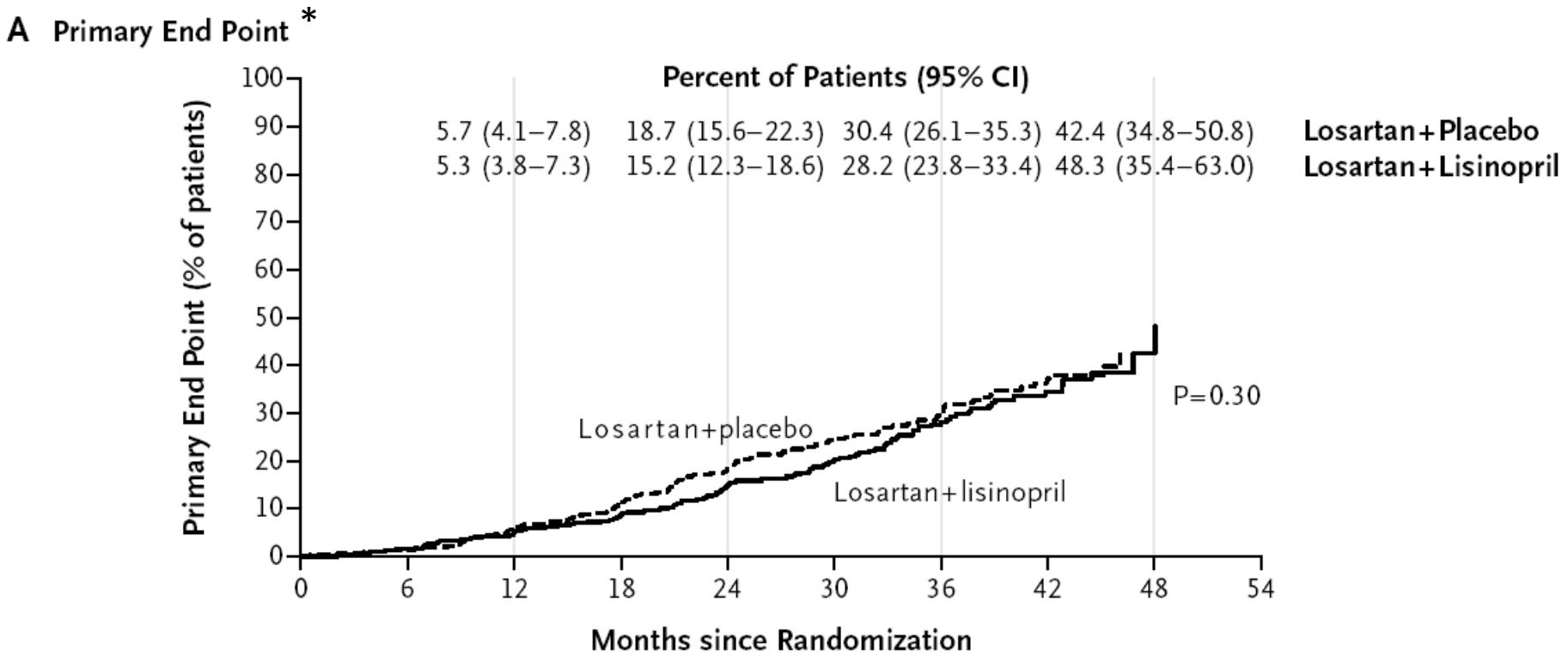
Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

Linda F. Fried, M.D., M.P.H., Nicholas Emanuele, M.D., Jane H. Zhang, Ph.D., Mary Brophy, M.D., Todd A. Conner, Pharm.D., William Duckworth, M.D., David J. Leehey, M.D., Peter A. McCullough, M.D., M.P.H., Theresa O'Connor, Ph.D., Paul M. Palevsky, M.D., Robert F. Reilly, M.D., Stephen L. Seliger, M.D., Stuart R. Warren, J.D., Pharm.D., Suzanne Watnick, M.D., Peter Peduzzi, Ph.D., and Peter Guarino, M.P.H., Ph.D., for the VA NEPHRON-D Investigators*

We provided losartan (at a dose of 100 mg per day) to patients with type 2 diabetes, a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 300, and an estimated glomerular filtration rate (GFR) of 30.0 to 89.9 ml per minute per 1.73 m^2 of body-surface area and then randomly assigned them to receive lisinopril (at a dose of 10 to 40 mg per day) or placebo.

Fried LF et al, N Engl J Med 9.Nov 2013

VA-Nephron-D Studie: **Losartan vs. Losartan + Lisinopril**



No. at Risk

Losartan+placebo	724	641	543	453	335	238	149	75	14
Losartan+lisinopril	724	631	534	457	347	245	139	69	10

* eGFR-Abfall ≥30 ml/min/1.73 m² falls eGFR ≥6 oder ≥50% falls eGFR <60, terminales Nierenversagen oder Tod

Fried LF et al, N Engl J Med 9.Nov 2013

VA-Nephron-D Studie: **Losartan vs. Losartan + Lisinopril**

Table 3. Safety Outcomes.*

Outcome	Losartan plus Placebo (N=724)	Losartan plus Lisinopril (N=724)	Hazard Ratio with Losartan plus Lisinopril (95% CI)	P Value
Patients with serious adverse events — no. (%)	380 (52.5)	416 (57.5)	NA	0.06
No. of serious adverse events	1274	1539†	NA	
Attribution of serious adverse events to study drugs — no. of events (%)†				0.049
Not attributed	1159 (91.0)	1365 (88.7)	NA	
Possibly attributed	104 (8.2)	146 (9.5)	NA	
Attributed	11 (0.9)	27 (1.8)	NA	
Acute kidney injury — no. of patients (%)	80 (11.0)	130 (18.0)	1.7 (1.3–2.2)	<0.001
Hyperkalemia — no. of patients (%)	32 (4.4)	72 (9.9)	2.8 (1.8–4.3)	<0.001

Pergola PE et al, N Engl J Med 2011, 24. Juni

Bardoxolon-Therapie in Typ II Diabetikern mit CKD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

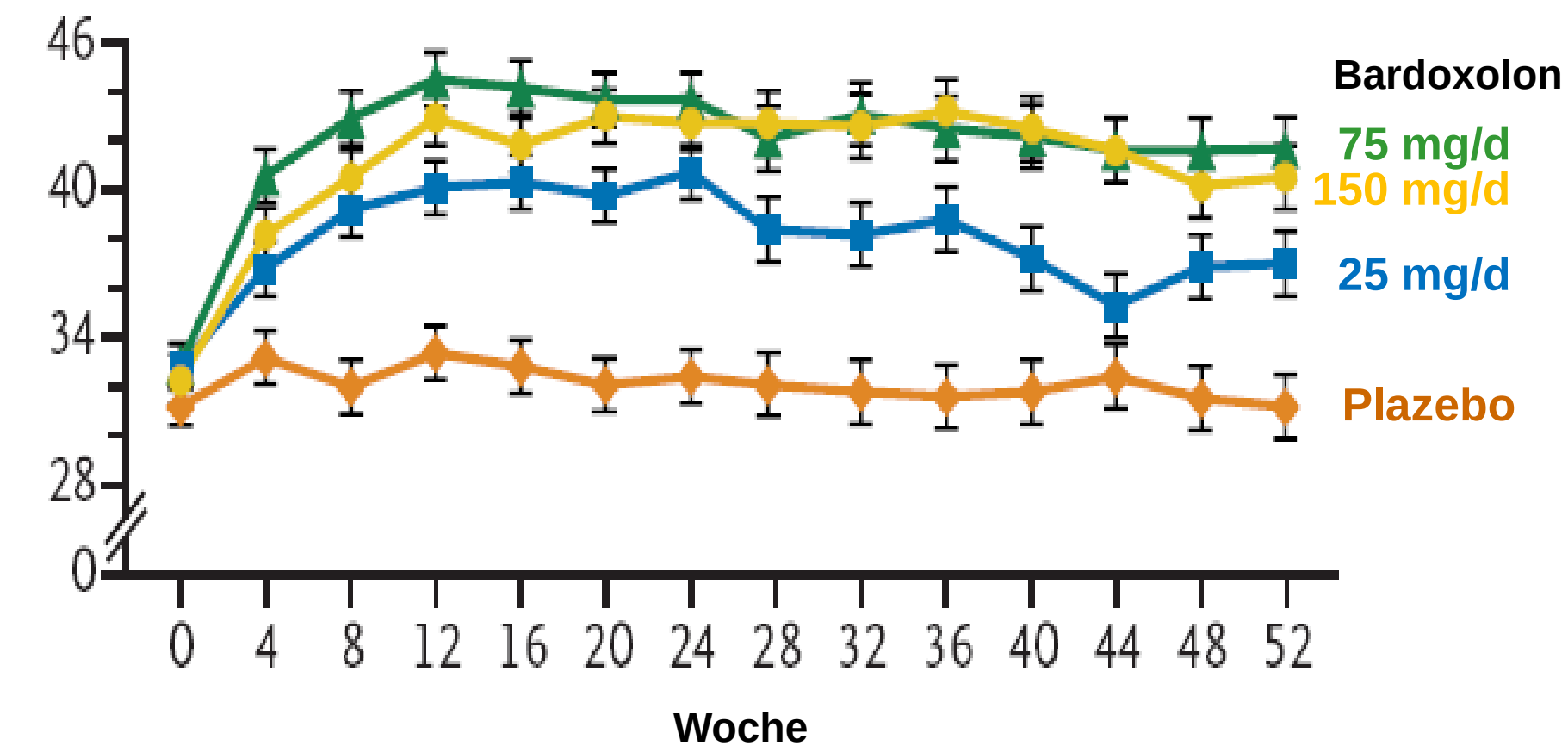
Bardoxolone Methyl and Kidney Function in CKD with Type 2 Diabetes

Pablo E. Pergola, M.D., Ph.D., Philip Raskin, M.D., Robert D. Toto, M.D., Colin J. Meyer, M.D., J. Warren Huff, J.D., Eric B. Grossman, M.D., Melissa Krauth, M.B.A., Stacey Ruiz, Ph.D., Paul Audhya, M.D., Heidi Christ-Schmidt, M.S.E., Janet Wittes, Ph.D., and David G. Warnock, M.D., for the BEAM Study Investigators*

Pergola PE et al, N Engl J Med 2011, 24. Juni

Diabetiker mit CKD

BEAM: Bardoxolon-Therapie in Typ II Diabetikern mit CKD



Ca. 10% Gewichtsverlust unter Bardoxolon!
=> Wie valide ist Kreatinin-basierte eGFR Messung?

N Engl J Med 2013, 9. Nov.

BEACON: Bardoxolon-Therapie in Typ II Diabetikern mit CKD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

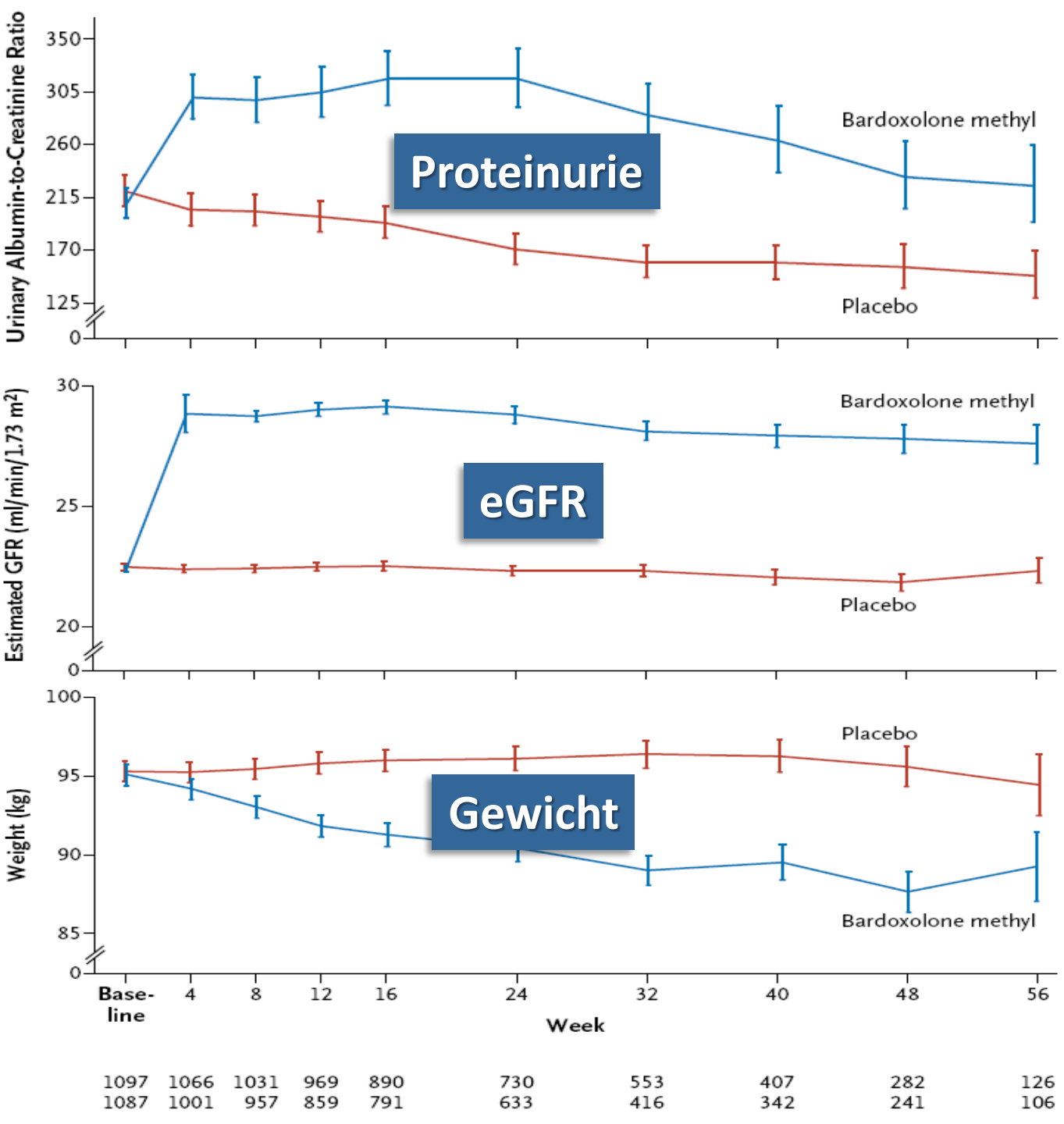
Bardoxolone Methyl in Type 2 Diabetes and Stage 4 Chronic Kidney Disease

Dick de Zeeuw, M.D., Ph.D., Tadao Akizawa, M.D., Ph.D., Paul Audhya, M.D., M.B.A., George L. Bakris, M.D., Melanie Chin, Ph.D., Heidi Christ-Schmidt, M.S.E., Angie Goldsberry, M.S., Mark Houser, M.D., Melissa Krauth, M.B.A., Hiddo J. Lambers Heerspink, Pharm.D., Ph.D., John J. McMurray, M.D., Colin J. Meyer, M.D., Hans-Henrik Parving, M.D., D.M.Sc., Giuseppe Remuzzi, M.D., Robert D. Toto, M.D., Nosratola D. Vaziri, M.D., Christoph Wanner, M.D., Janet Wittes, Ph.D., Danielle Wrolstad, M.S., and Glenn M. Chertow, M.D., M.P.H., for the BEACON Trial Investigators*

Diabetiker mit CKD

De Zeeuw D et al, N Engl J Med 2013, 9. Nov

BEACON: Bardoxolon-Therapie in Typ II Diabetikern mit CKD

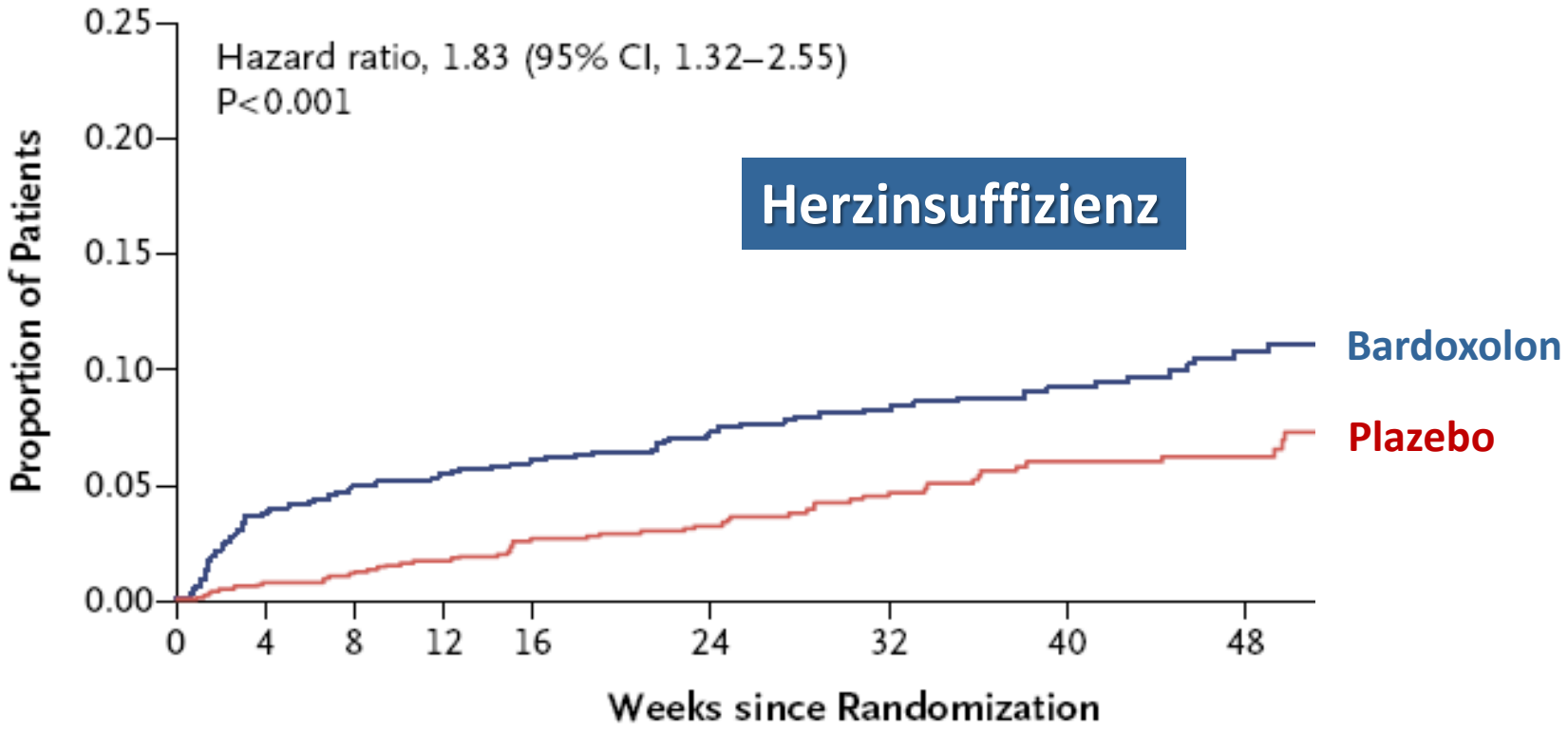


De Zeeuw D et al, N Engl J Med 2013, 9. Nov

Diabetiker mit CKD

BEACON: Bardoxolon-Therapie in Typ II Diabetikern mit CKD

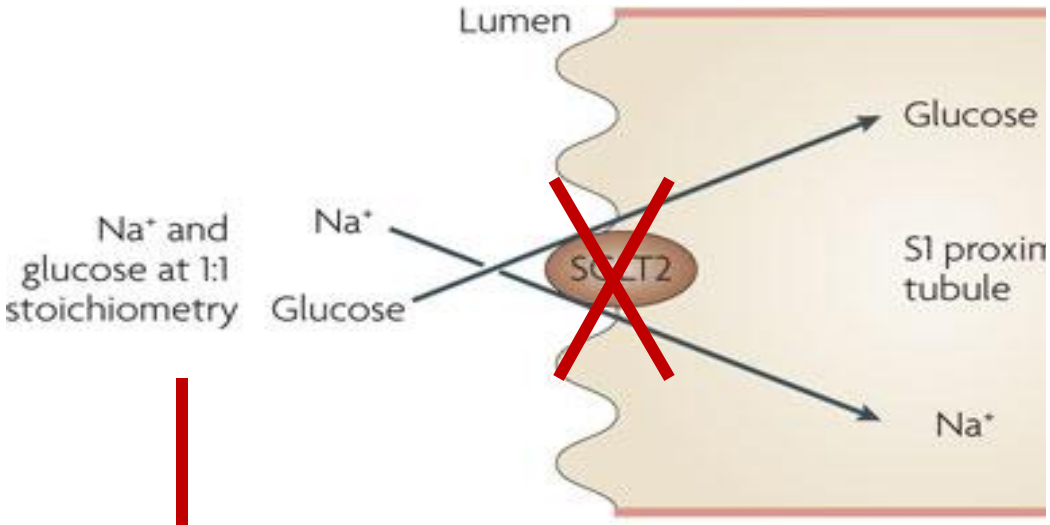
Among patients with type 2 diabetes mellitus and stage 4 chronic kidney disease, bardoxolone methyl did not reduce the risk of ESRD or death from cardiovascular causes. A higher rate of cardiovascular events with bardoxolone methyl than with placebo prompted termination of the trial. (Funded by Reata Pharmaceuticals; BEACON ClinicalTrials.gov number, NCT01351675.)



Chao and Henry, Nature Reviews Drug Discovery 2010; 9, 551-559

Rationale einer SGLT2 Hemmung

Familiäre Renale Glukosurie



Phänotyp:
- Polyurie
- Dehydration (besonders in der Schwangerschaft)
- Häufiger Harnwegsinfekte

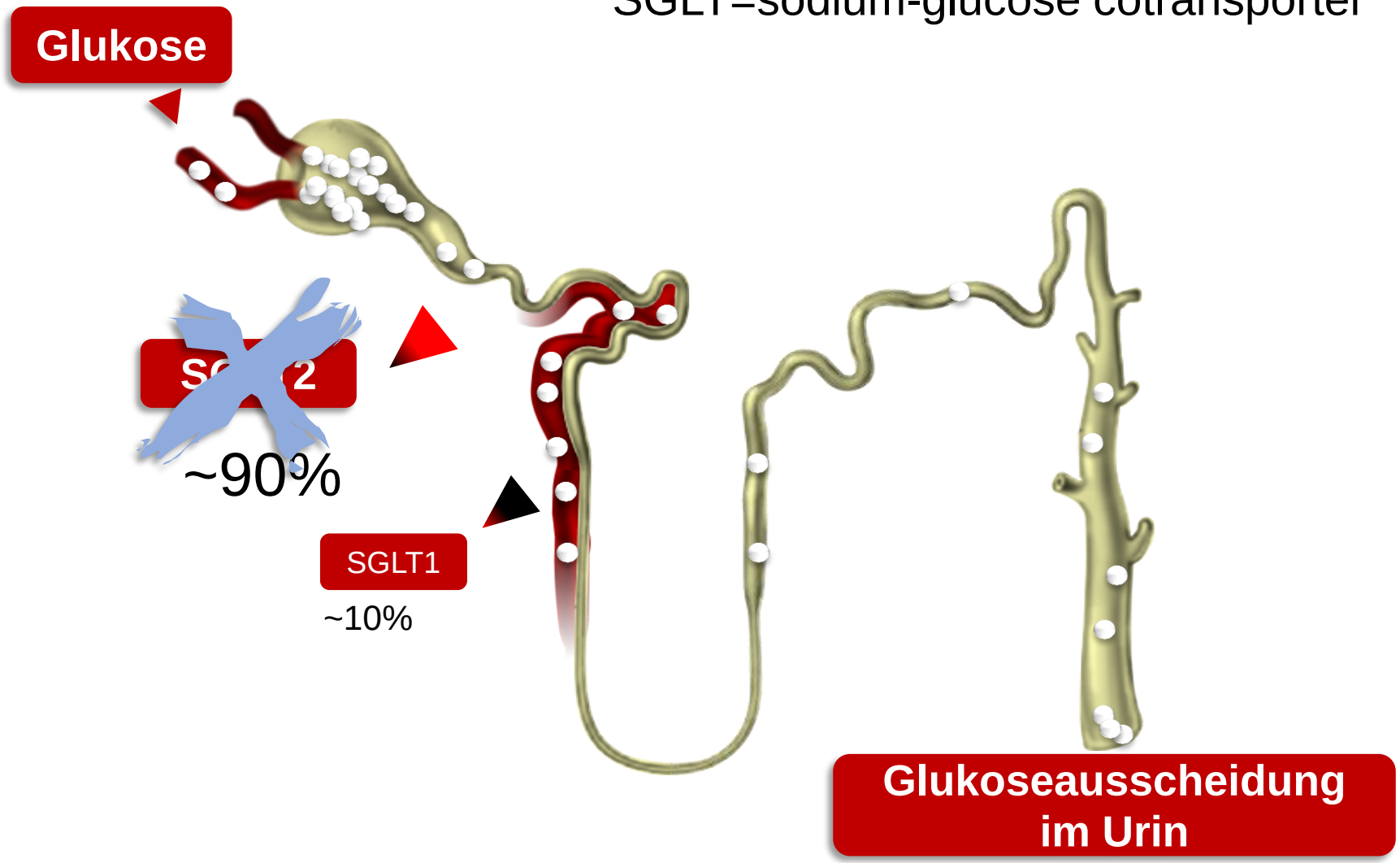
Vermehrte Glukose-Ausscheidung ohne Krankheitswert

Humane *loss of function* Mutation

Nature Reviews | Drug Discovery

Wirkung von SGLT2 Inhibitoren: gesteigerte Glukosurie durch SGLT2-Hemmung

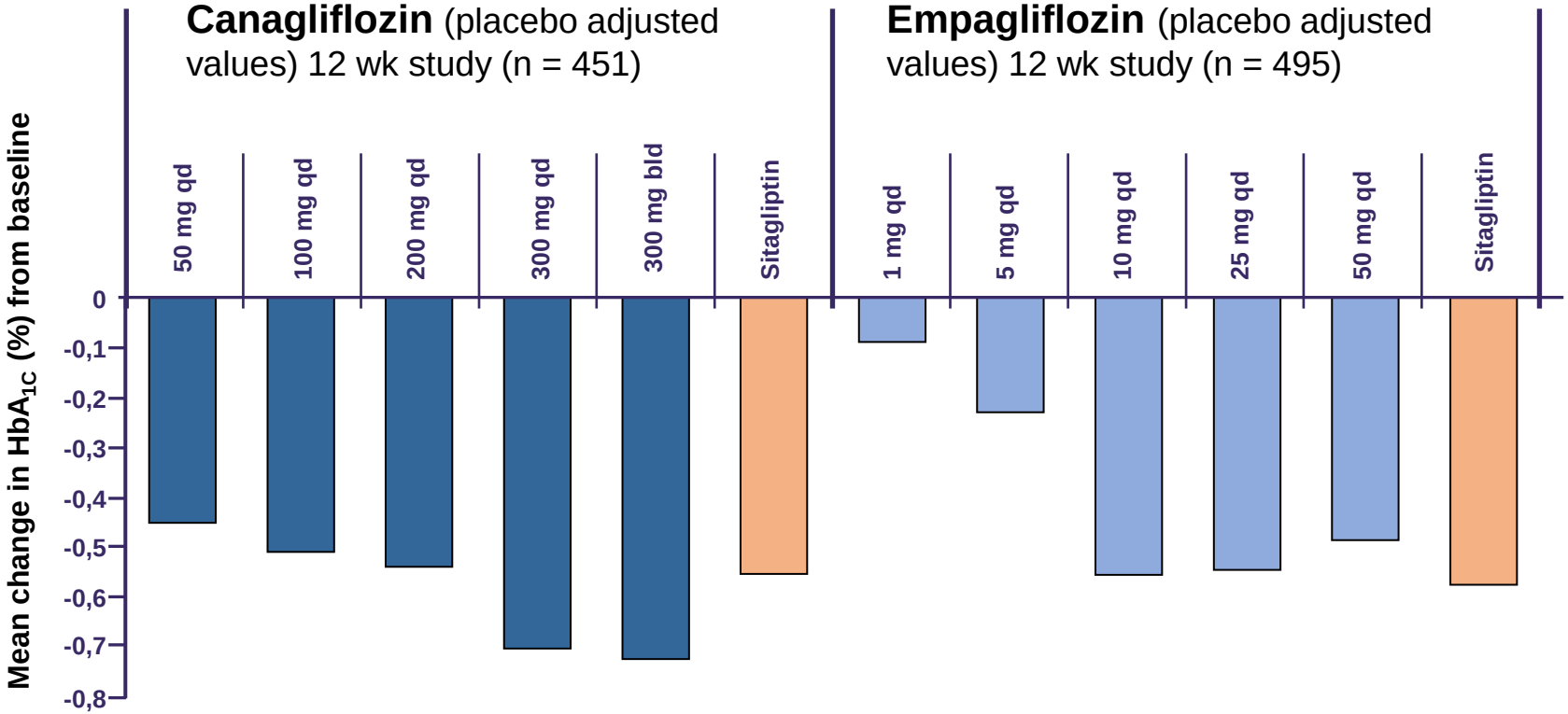
SGLT=sodium-glucose cotransporter



Zur Zeit in Entwicklung befindliche / zugelassene SGLT2-Inhibitioren

Name	Lead company	
Dapagliflozin	Bristol-Myers Squibb / AZ	Forxiga®
Empagliflozin (BI 10773)	Boehringer Ingelheim	
Canagliflozin	Johnson & Johnson	Invokana™
Ipragliflozin (ASP1941)	Astellas Pharma	
LX4211*	Lexicon Pharmaceuticals	
BI 44847	Boehringer Ingelheim	
Tofogliflozin (CSG452)	Chugai Pharmaceutical	
PF-04971729	Pfizer	
TS-071	Taisho Pharmaceutical	
ISIS-SGLT2Rx	Isis Pharmaceuticals	

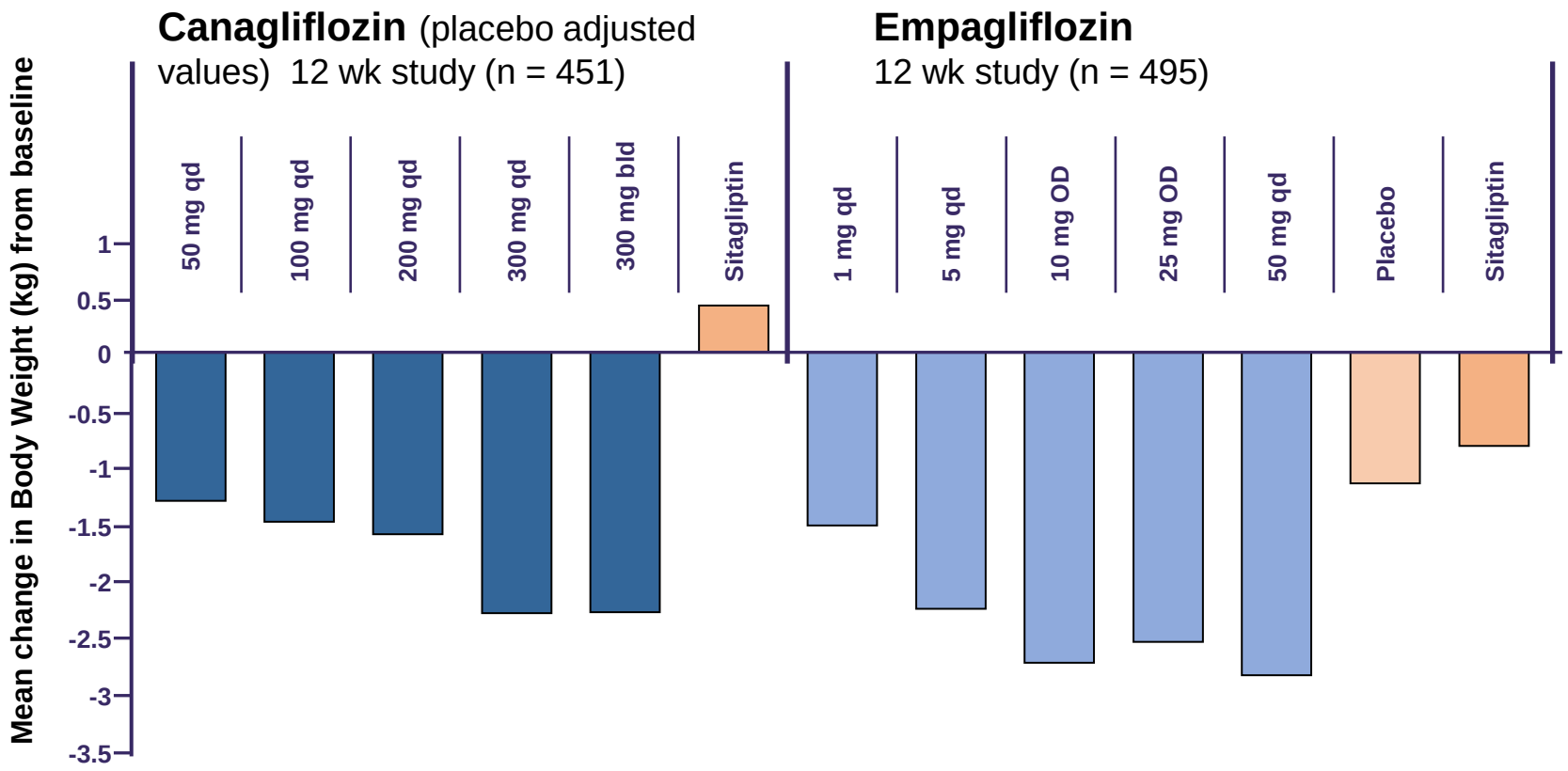
Veränderung des HbA_1C nach 12 Wochen SGLT2-Inhibition bei bestehender Metformin-Therapie



Baseline HbA_{1C} (%) **7.7** **7.9**

Rosenstock J et al. Diabetologia 2010; 53 (Suppl 1): S349;
Seman L et al. Presented at EASD Annual Meeting, Lisbon 12-16 September 2011; abstract #147

Veränderung des Gewichts nach 12 Wochen SGLT2-Inhibition bei bestehender Metformin-Therapie



Baseline Körpergewicht: 87 kg

Rosenstock J et al. Diabetologia 2010; 53 (Suppl 1): S349;
Seman L et al. Presented at EASD Annual Meeting, Lisbon 12-16 September 2011; abstract #147

Wirkung von SGLT2-Inhibitoren an der Niere - experimentelle Daten

Potentiell nephroprotektive Effekte:

- Verminderung der glomerulären Hyperfiltration
- Senkung der S-Harnsäure
- Längere Lebensfähigkeit der proximalen Tubuluszellen durch begrenzte Glukoseaufnahme
- Blutdrucksenkung (ca. 5 mmHg)

Stanton Circulation, 2013

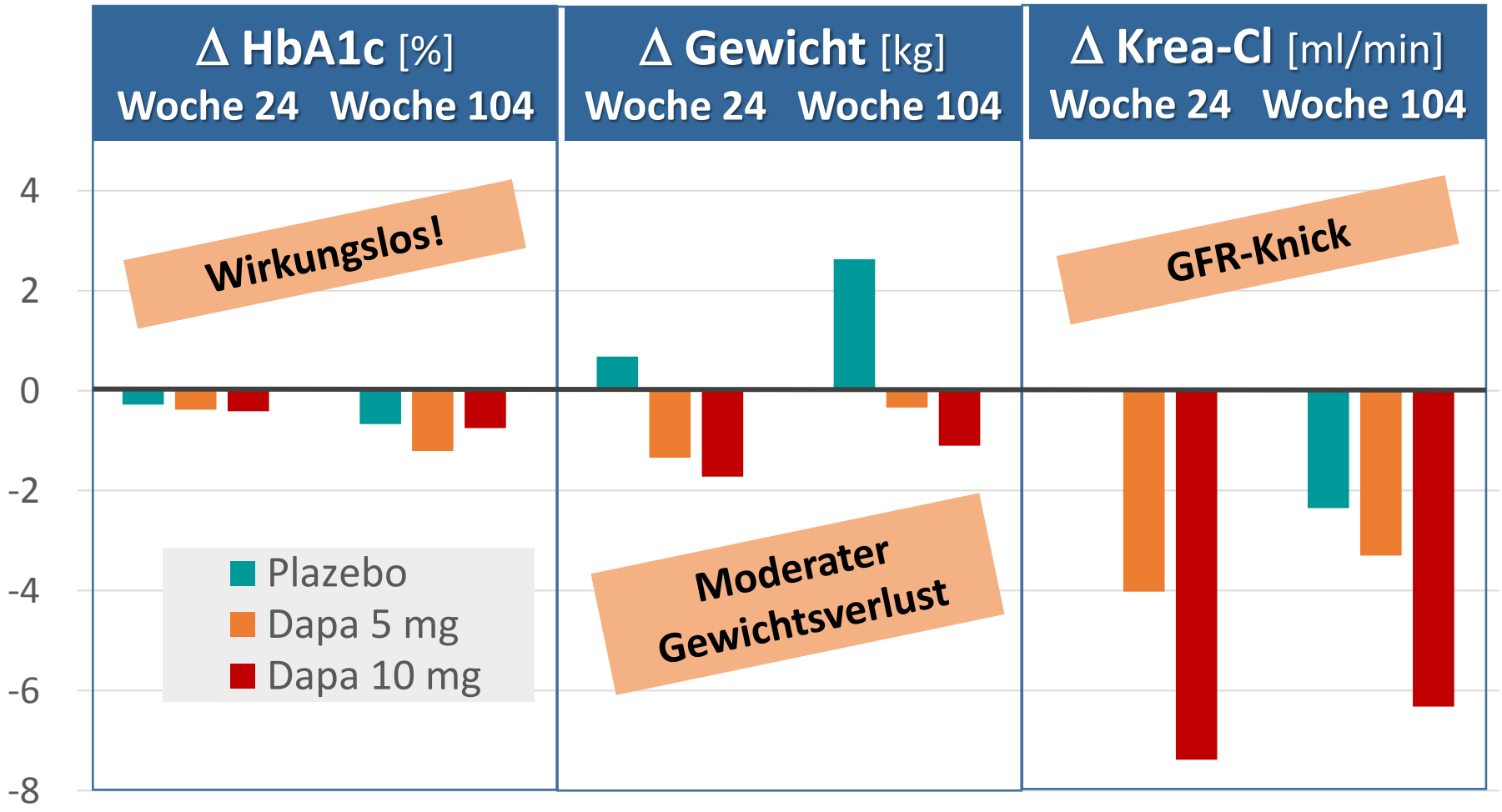
Kardiovaskuläre Outcome Studien mit SGLT2 Hemmern

Study	Drug	Population	Results
DECLARE – TIMI 58	Dapagliflozin vs. placebo	17150 pts, T2D at high CV risk	2018
CANVAS	Canagliflozin vs. placebo	4330 pts, T2D at high CV risk	2018
EMPA-REG OUTCOME	Empagliflozin vs placebo	7000 pts, T2D at high CV risk	2018

http://clinicaltrials.gov/

Kohan DE et al, Kidney International 2014;85: 962–97.

2 Jahre Dapagliflozin bei Diabetikern mit CKD 2-4



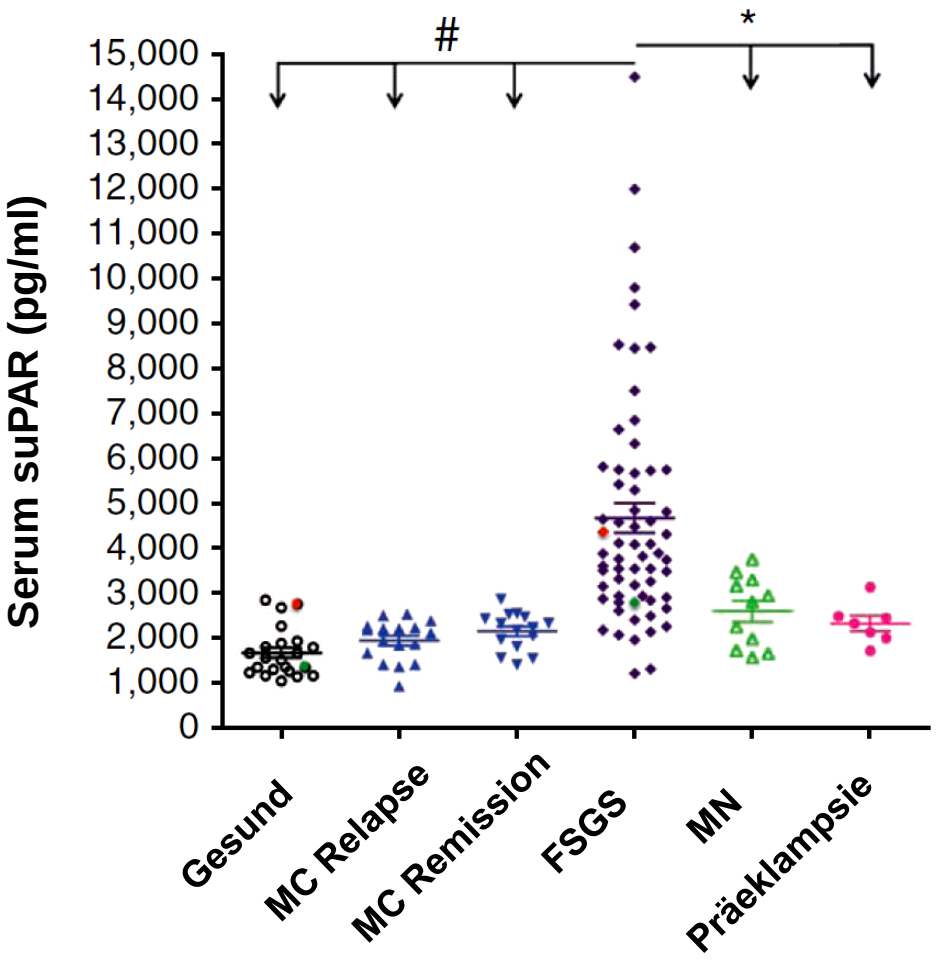
MCNS
FSGS

Wei C et al. Nat Med. 2011; 17: 952-60

Zikulierender Urokinaserezeptor (suPAR) als Ursache der FSGS

löslicher, zirkulierender Urokinaserezeptor

- in geringer Konzentration physiologisch im Serum nachweisbar
- Rolle in Neutrophilen- und Stammzell-Mobilisation
- Überexpression von uPAR in Podozyten induziert Fußfortsatz-Verschmelzung + Proteinurie via Interaktion mit ß3-Integrin (Wei C et al, Nat Med 2008)



Ein suPAR Requiem…

Kidney International März 2014

CLINICAL INVESTIGATION ▲ Top

The soluble urokinase receptor is not a clinical marker for focal segmental glomerulosclerosis FREE

Björn Meijers, Rutger J H Maas, Ben Sprangers, Kathleen Claes, Ruben Poesen, Bert Bammens, Maarten Naesens, Jeroen K J Deegens, Ruth Dietrich, Markus Storr, Jack F M Wetzels, Pieter Evenepoel and Dirk Kuypers

Kidney Int 85: 636-640; advance online publication, January 8, 2014; doi:10.1038/ki.2013.505

Abstract | Full Text | PDF

See also: Commentary by Schlöndorff

A multicenter cross-sectional study of circulating soluble urokinase receptor

Takehiko

Sawako K

Keiji Fujin

Yoshie Sa

Kidney Int

Abstract | F

See also: C

Serum-s glomeru children

Aditi Sinh

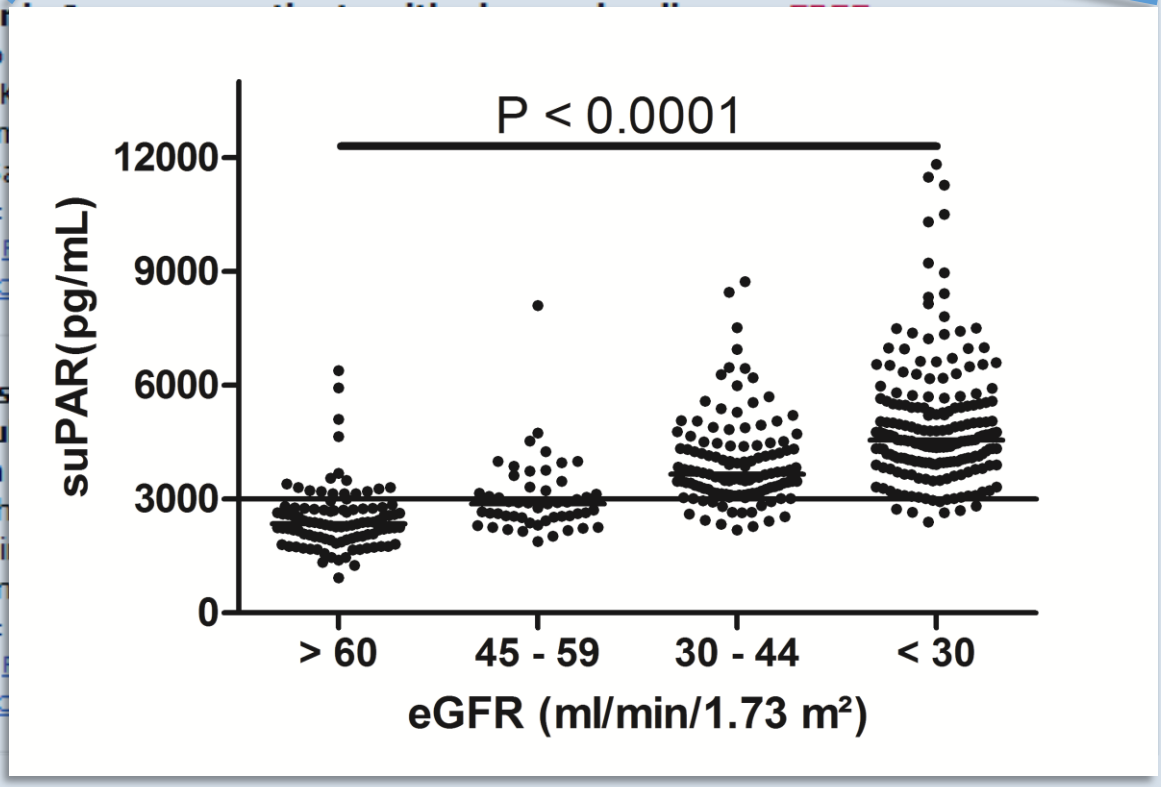
Amit K Di

and Arvin

Kidney Int

Abstract | F

See also: C



Stone et al, NEJM, 2010; Jones et al., NEJM 2010

Anti-B-Zell-Therapie (Rituximab): Remissionsinduktion bei ANCA Vaskulitis

RAVE

Rituxi 4 x 375 mg/m^2 + Pred (6Mo) n = 99, ED/ Rezidiv BVAS WG 8,5; GFR 54 ml/min	Cyclophosphamid tgl. p.o. 2 mg/kg + Pred (6 Mo) n = 98, ED/Rezidiv BVAS WG 8,2; GFR 69 ml/min

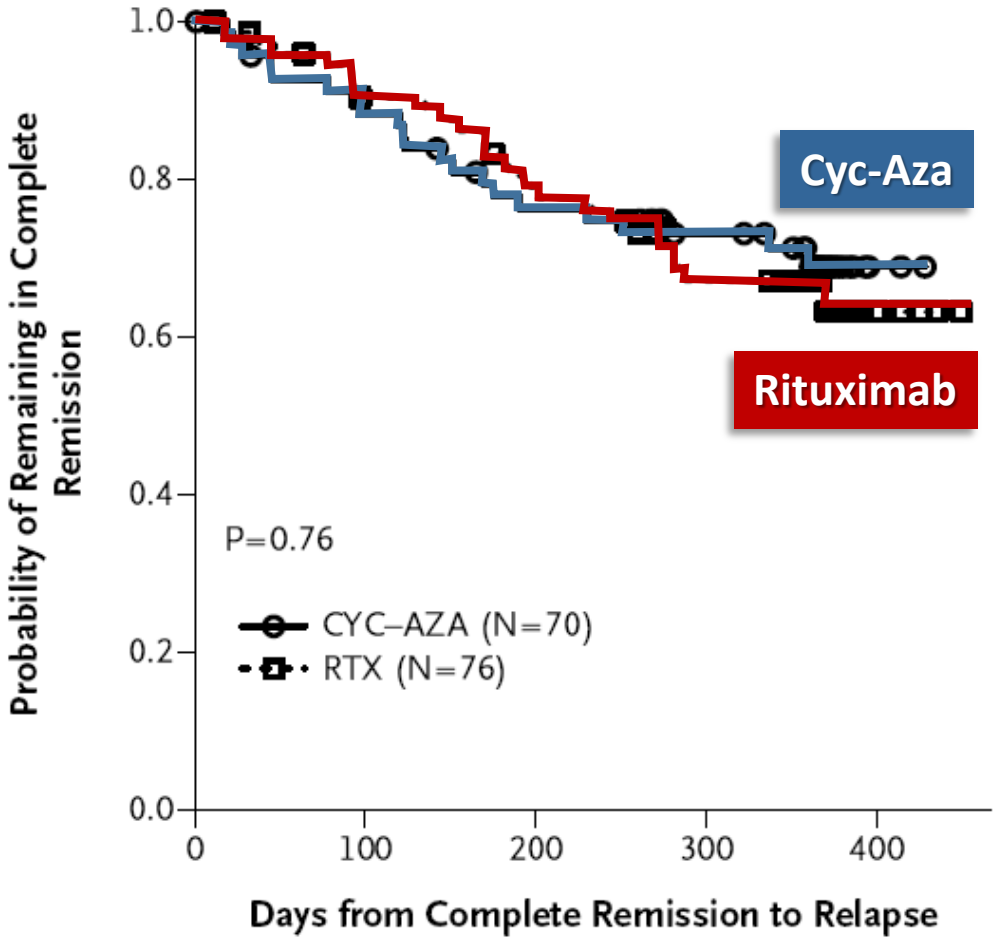
RITUXVAS

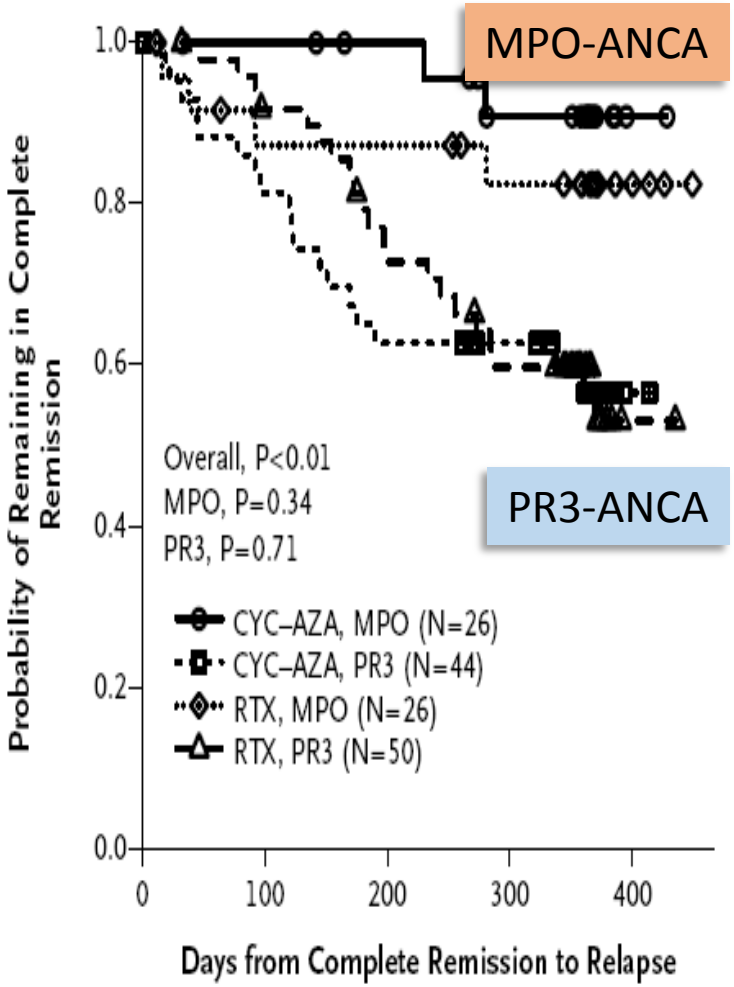
Rituxi 4 x 375 mg/m^2 + 1 Cyc Puls + Pred (12 Mo) n = 33, ED BVAS 19; GFR 20 ml/min	Cyc Puls i.v. nach CYCLOPS + Pred (12 Mo) n = 11, ED BVAS 18 GFR 12 ml/min
↓	↓
Keine Remissionserhaltung	Azathioprin 2 mg/kg

Σ Rituximab CYC nicht unterlegen, für Rezidiv-Therapie überlegen!
Kein Unterschied bzgl. Todesfälle, schwere Infektionen, Rezidive

Rituximab bei ANCA-Vaskulitis
RAVE-Studie: Status nach 18 Monaten

Specks U et al, N Engl J Med 2013;369:417-27

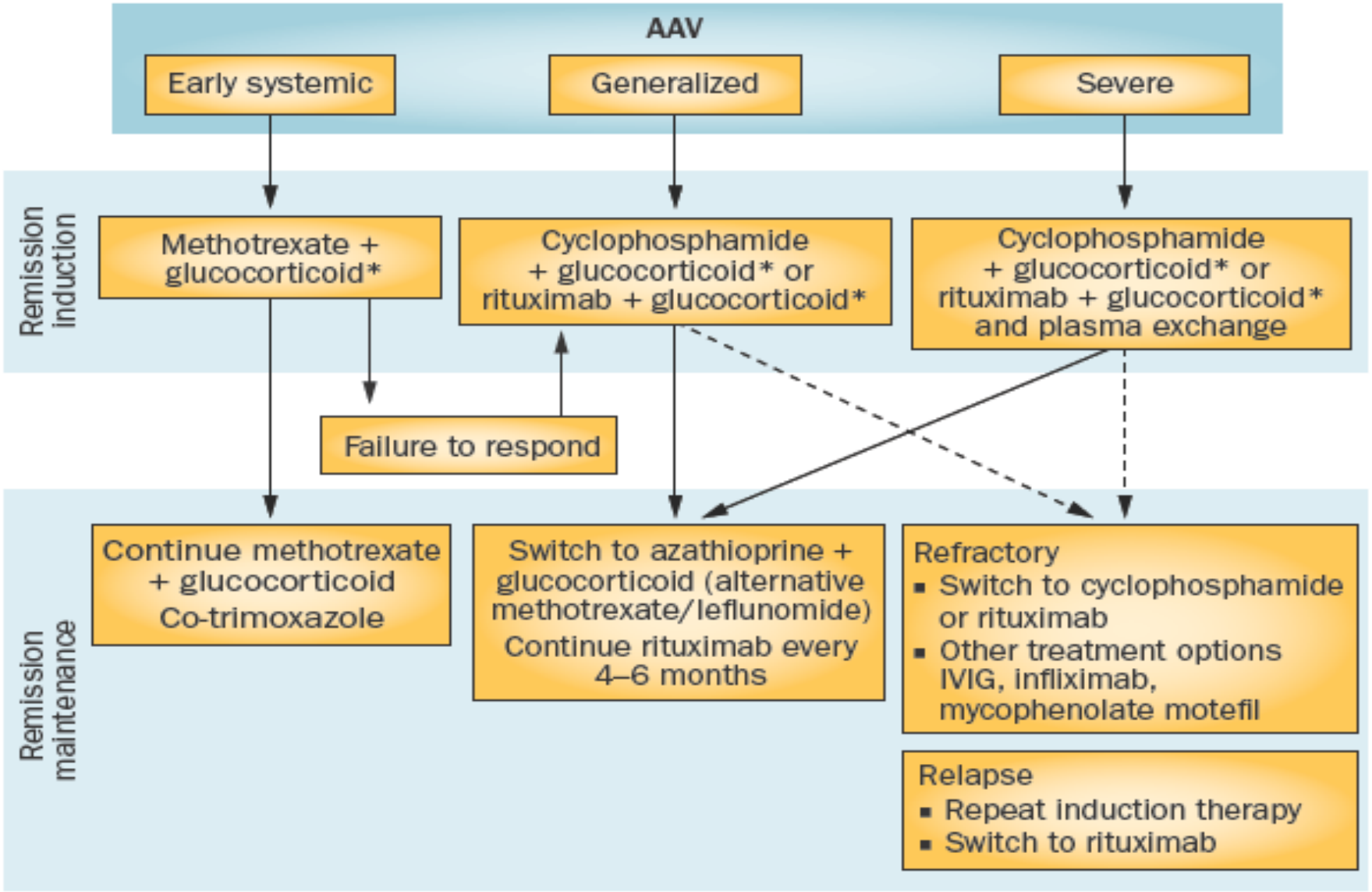




No. at Risk					
CYC–AZA	70	61	51	43	3
RTX	76	65	55	45	5

Schoenermarck M et al, Nat Rev Nephrol 2014

Therapiealgorithmus

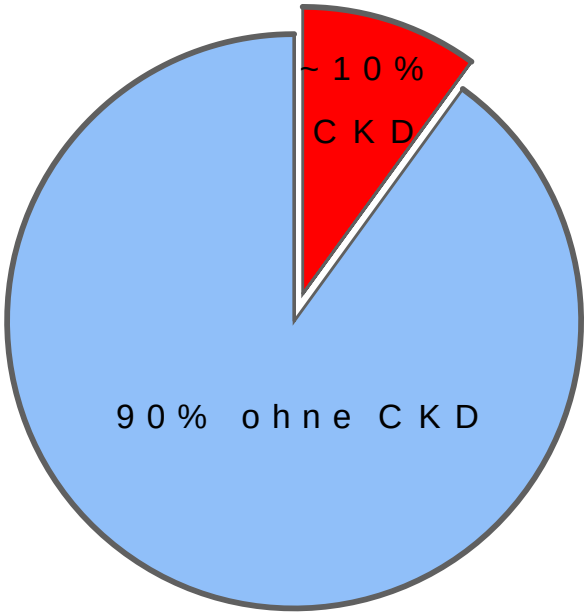


http://www.cdc.gov/diabetes/pubs/pdf/kidney_factsheet.pdf

Adams KF et al. Am Heart J 149, 209-215, 2005

Akute Herzinsuffizienz mit erhöhter CKD Prävalenz

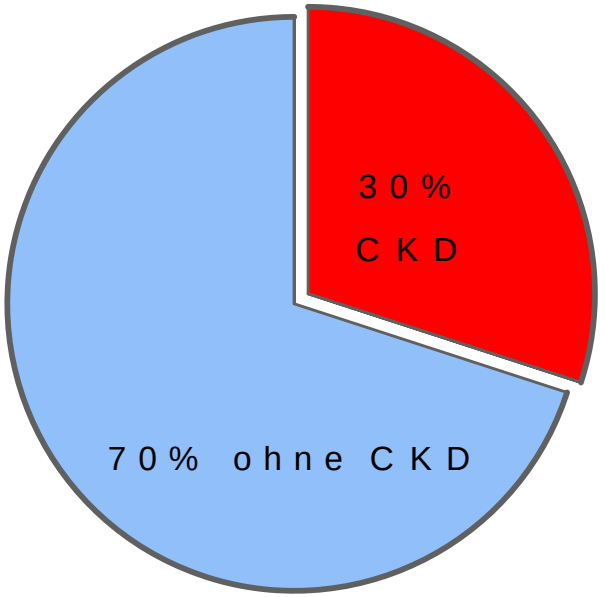
US Population



Acute Decompensated Heart Failure National Registry

ADHERE

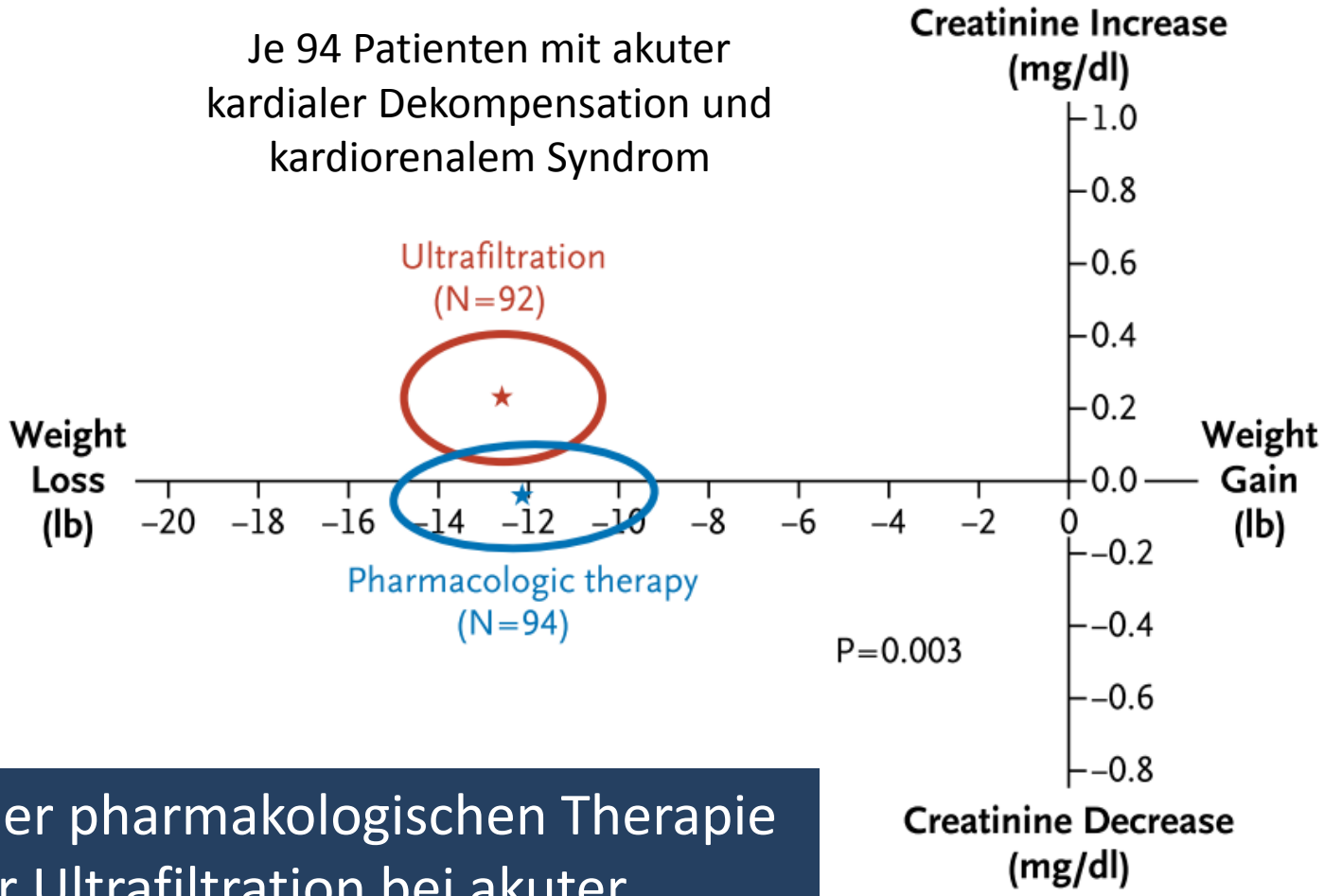
>100.000 US Bürger mit akuter kardialer Dekompensation



Bart et al., NEJM 2012

Herzinsuffizienz & CKD: Pharmakologie vs. Ultrafiltration?

Je 94 Patienten mit akuter kardialer Dekompensation und kardiorenalem Syndrom

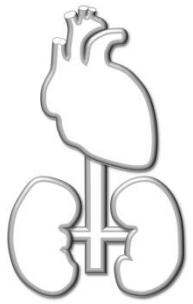


Überlegenheit der pharmakologischen Therapie gegenüber Ultrafiltration bei akuter dekompensierter Herzinsuffizienz und kardiorenalem Syndrom

Herz-/Nierenstation in der Uniklinik Aachen

Zunahme Herz- und Nieren-kranker Patienten

- 20 Betten (*Ziel 32*)
- Patienten mit Herz- & Nierenerkrankung
- Monitorüberwachung (Telemetrie)
- kardiologische & nephrologische Ärzte (Oberärzte & Assistenzärzte)
- Gemeinsame Pflegekräfte



Neue Phosphatbinder

- **Eisen-Zitrat** (Keryx Biopharmaceuticals)
- **Eisen(III)-Oxyhydroxid** (PA21; Vifor / Fresenius)

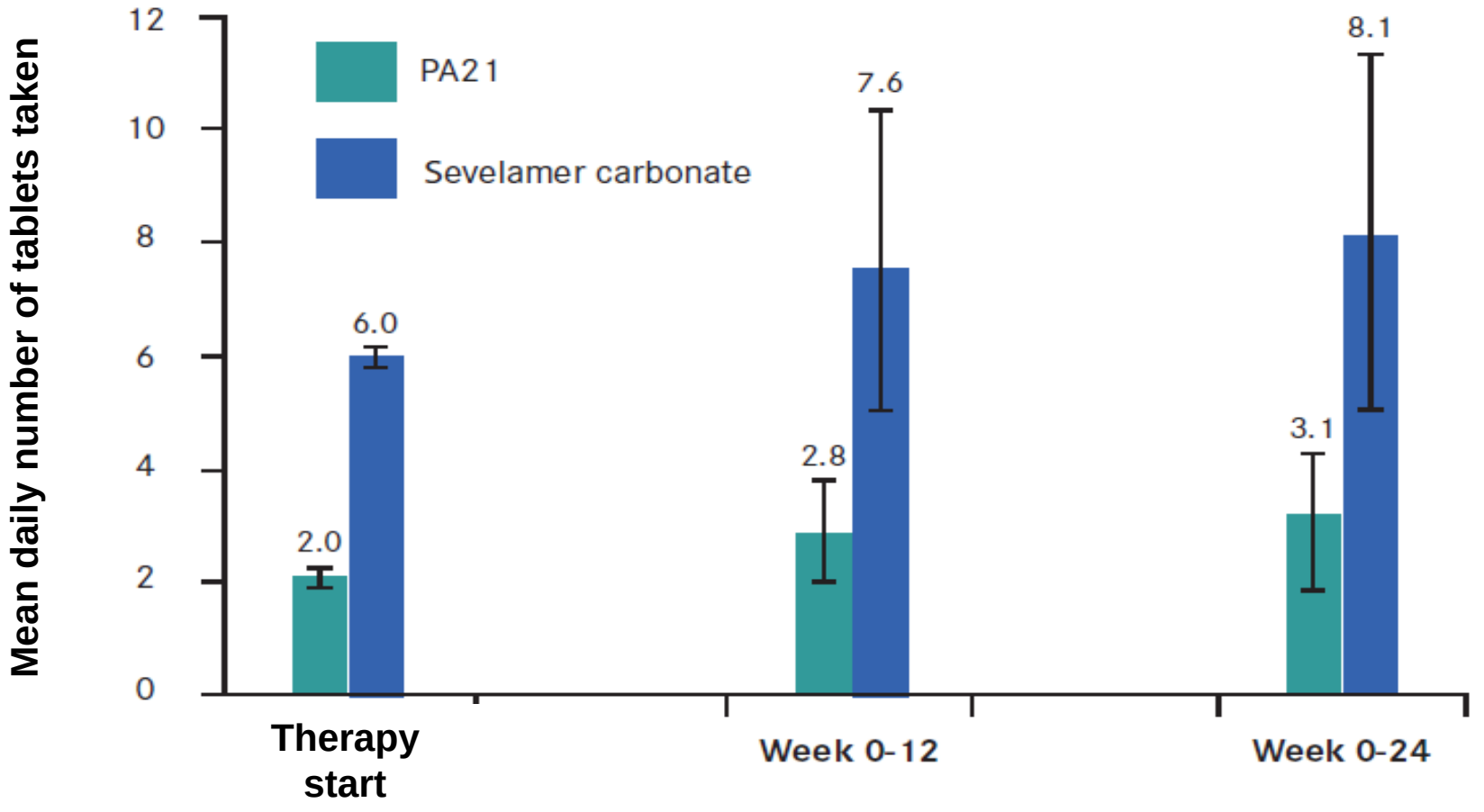
- **Polymer - Colestilan** (Mitsubishi)
  Zugelassen in Deutschland seit Anfang 2013

- **Nikotinamid** (Medice)
  NOPHOS (Phase III) Studie läuft

Floege J et al, Kidney Int 2014

PA21 Study PA-CL-05A: Pill Burden

Mean daily dose (g/day), Week 0-24	PA21 1.5 ± 0.6	SEVELAMER 6.5 ± 2.5



Dtsch Arztebl 2013; 110(45)
Freitag, 8. November 2013

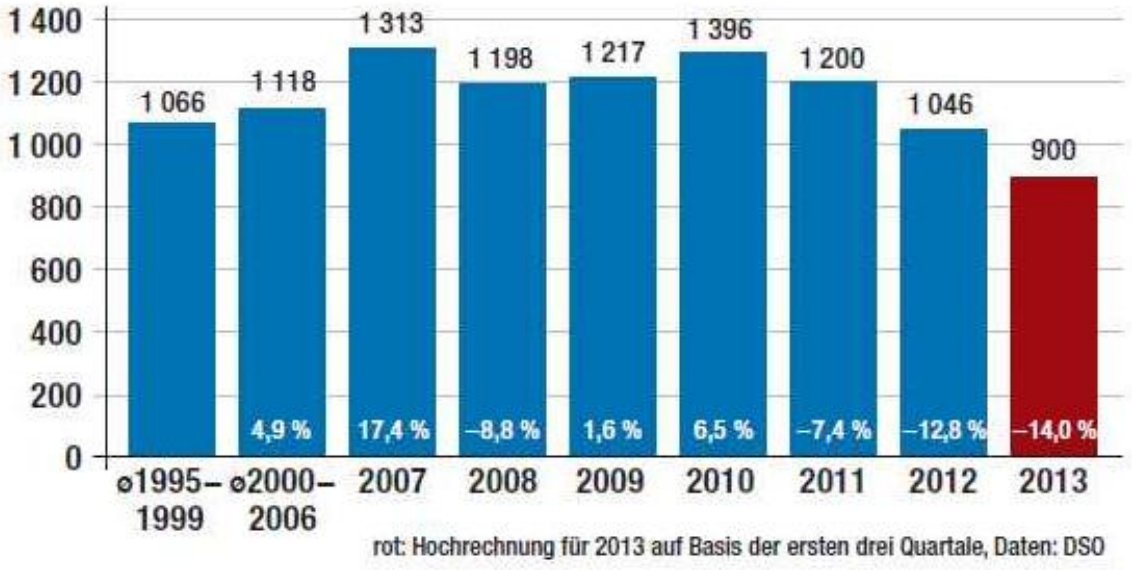
(nicht nur…)

Organspende-Skandal:

Einbruch der postmortalen Spenderzahlen

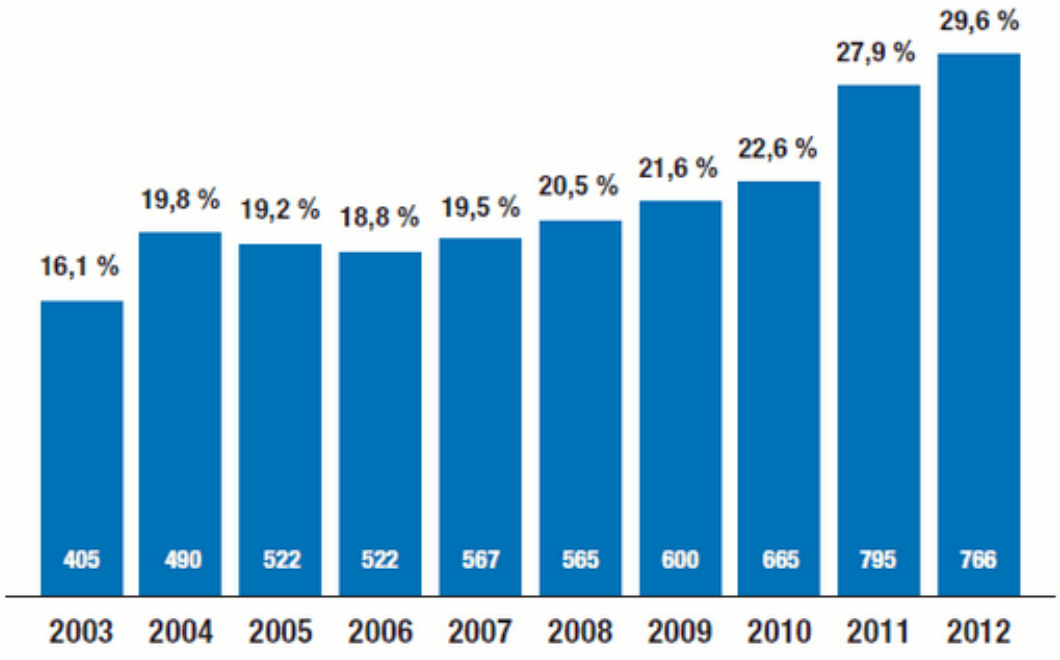
Anstieg der Lebendspenden

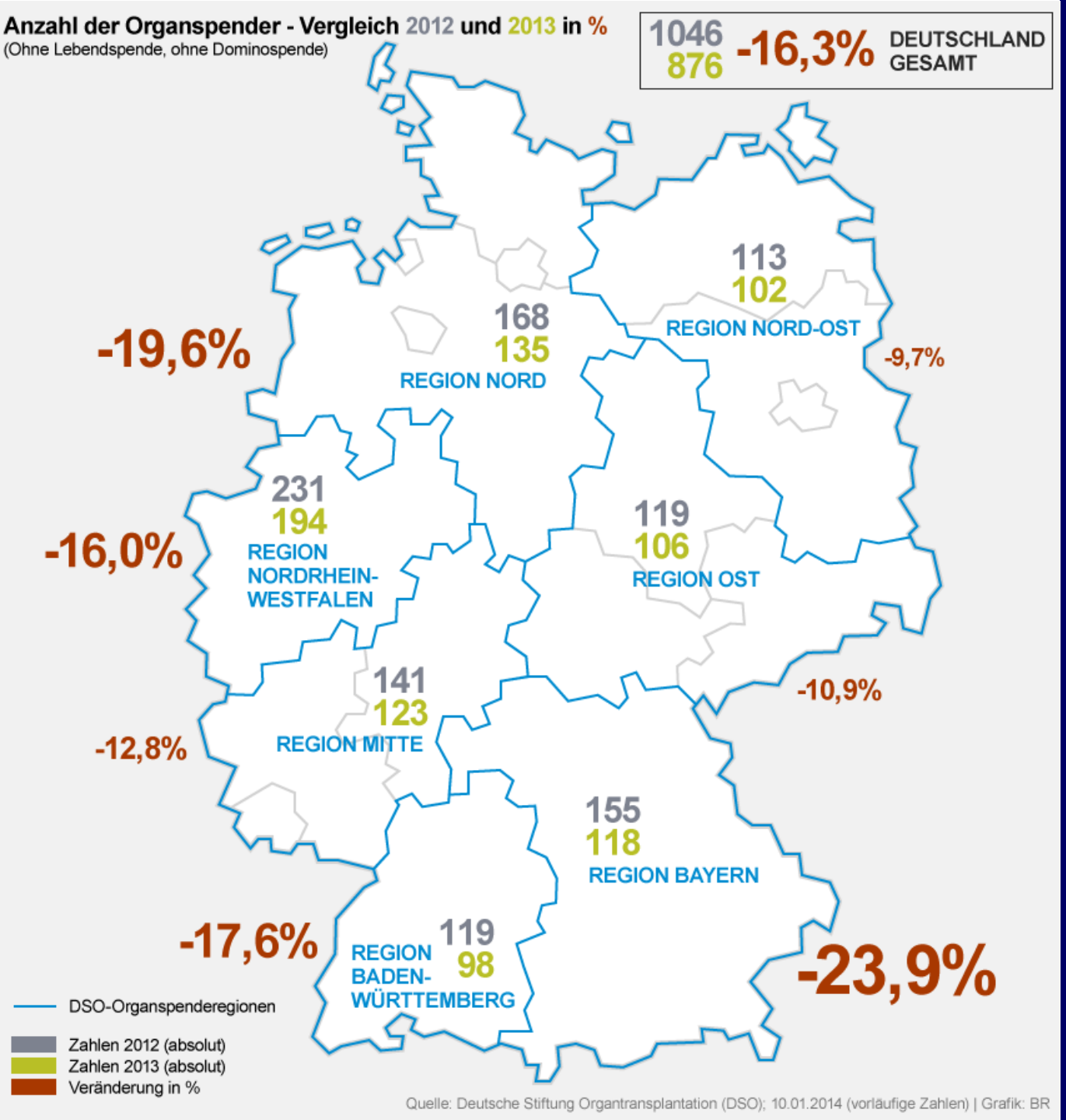
Postmortale Organspender in Deutschland (Veränderungen zum Vorjahr in %)



rot: Hochrechnung für 2013 auf Basis der ersten drei Quartale, Daten: DSO

Anteil der Lebendspenden an den Nierentransplantationen in Deutschland





DGfN Vorschlag zur Neustrukturierung:

Bundes-transplantations-zentrum

Vergütung nach Qualität

~~Schließung kleiner Zentren~~

Was hat Floege gesagt….?

Nephrologie allgemein	Neue KDIGO CKD-Leitlinien
Hypertonie	CORAL: atherosklerot. Nierenarterienstenose ☞ eher keine PTCA
Diabet. Nephropathie	NEPHRON-D: duale RAS-Blockade tot BEACON: Bardoxolon ⇨ Flüssigkeitsretention SGLT-2 Hemmer: spannend, eher nicht in CKD
GN / Vaskulitis	suPAR ist nicht super! Rituximab wie Cyc/Aza in ANCA-Vaskulitis
Herz & Niere	Kombinierte Kardio-Nephro-Station
Dialyse/Transplantation	Neue PO_4-Binder; TX leider kein Highlight….