Neue und bewährte Therapieoptionen bei resistenter Hypertonie

Nephrologische Praxis
Osnabrück Bramsche

Get it out of your heads, if possible, that the high pressure is the primary feature, and particularly the feature to treat

Sir William Osler 1912

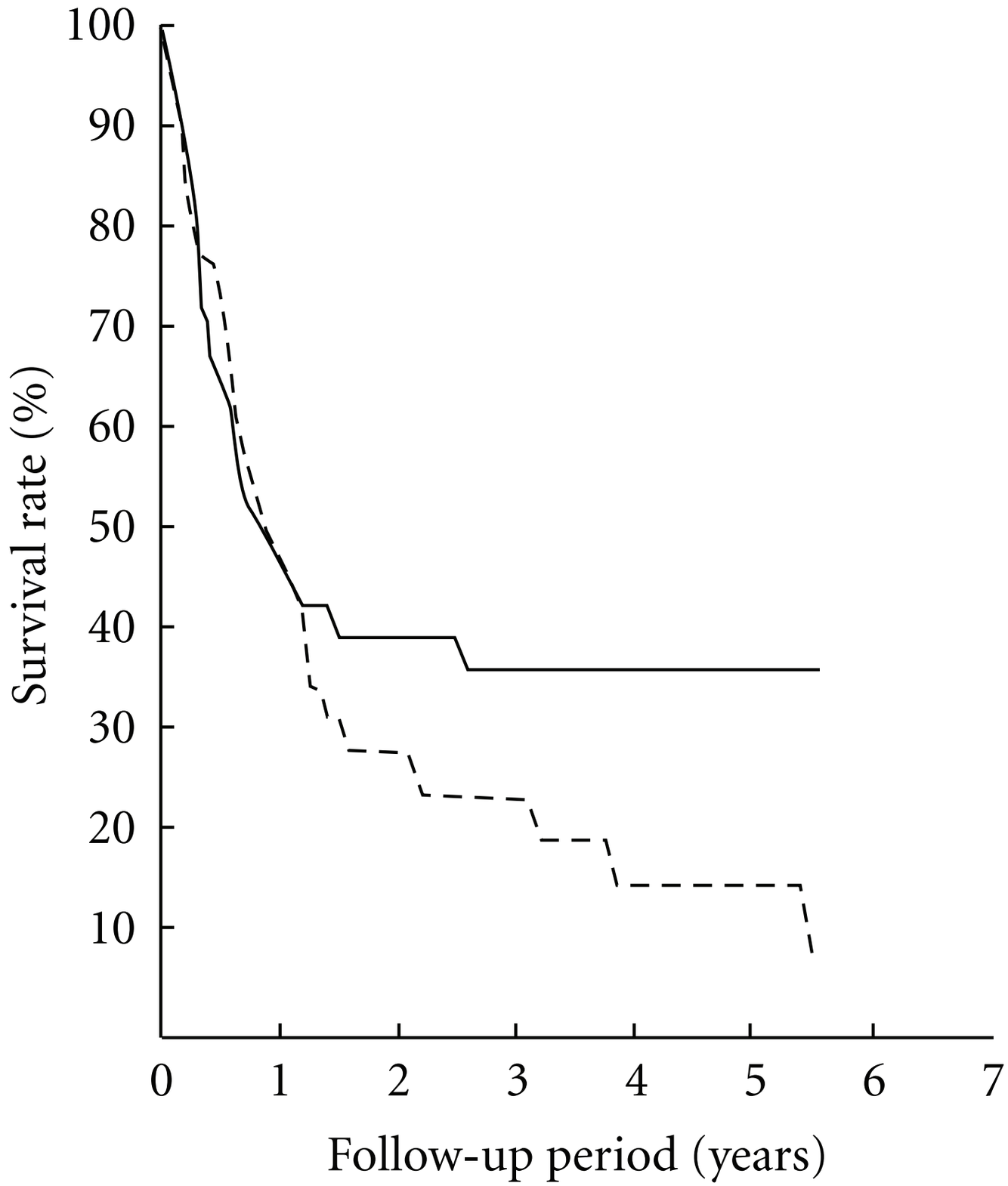

100
90
80
70
60
50
40
30
20
10
Survival rate (%)
0
1
2
3
4
5
6
7
Follow-up period (years)
Controlled SBP (< 160 mmHg)
Uncontrolled SBP (> 160 mmHg)

Table 2. Dates of Discovery of Antihypertensive Drugs or Drug Classes

Year(s)	Antihypertensive Agent(s)
1900	Sodium thiocyanate
1931	Reserpine
1947–1950	Ganglion blocking drugs
1958	Thiazide-type diuretics
1950s	Hydralazine
1950s	Guanethidine
1957	Spironolactone
1960	Methyldopa
1973	β-Receptor blockers (eg, propranolol)
1970s	Central α_2 agonists (eg, clonidine)
1975	Peripheral α_1 receptor blockers (eg, prazosin)
1977	ACE inhibitors (eg, captopril)
1977	Calcium channel blockers (eg, verapamil, nifedipine)
1993	Angiotensin II receptor blockers (eg, losartan)
2000	Renin inhibitors (eg, aliskiren)

ACE indicates angiotensin-converting enzyme. Data derived from Freis.[39]

1914: erste renale Denervation bei Nephralgie
1924: erste Sympathektomie

1966: erste Karotisstimulaton

HTN1 2009
HTN2 2010
HTN3 2016

Definition

Praxisblutdruck (mmHg)

RR > 140/80 / > 130/80

3 Antihypertensiva

incl. Diuretikum

ca. 9% resistente Hypertoniker

1,3 Milliarden Übergewichtige

1 Milliarde Hypertoniker

PSEUDORESISTENZ

Arzt

Patient

falsche Blutdruckmessung

Fehler im Blutdruckmanagement

Nicht Erkennen/fehlende Abklärung sek. RR Formen

ineffektive Kombinationen

inadäquate Dosis (Nebenwirkungen)

Blutdruck steigernde Medikamente

schlechte Adherenz

Salzexzess

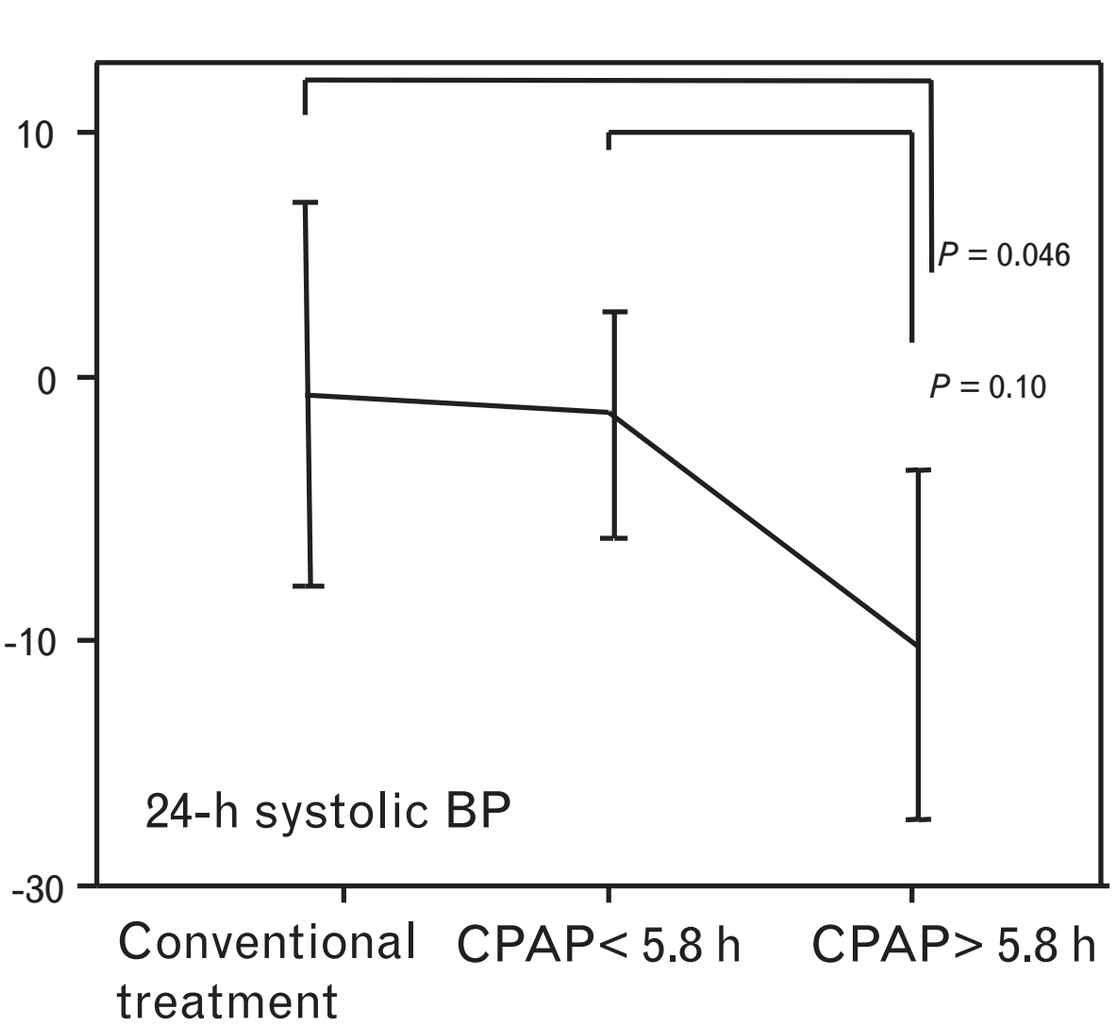
Sekundäre RR Formen

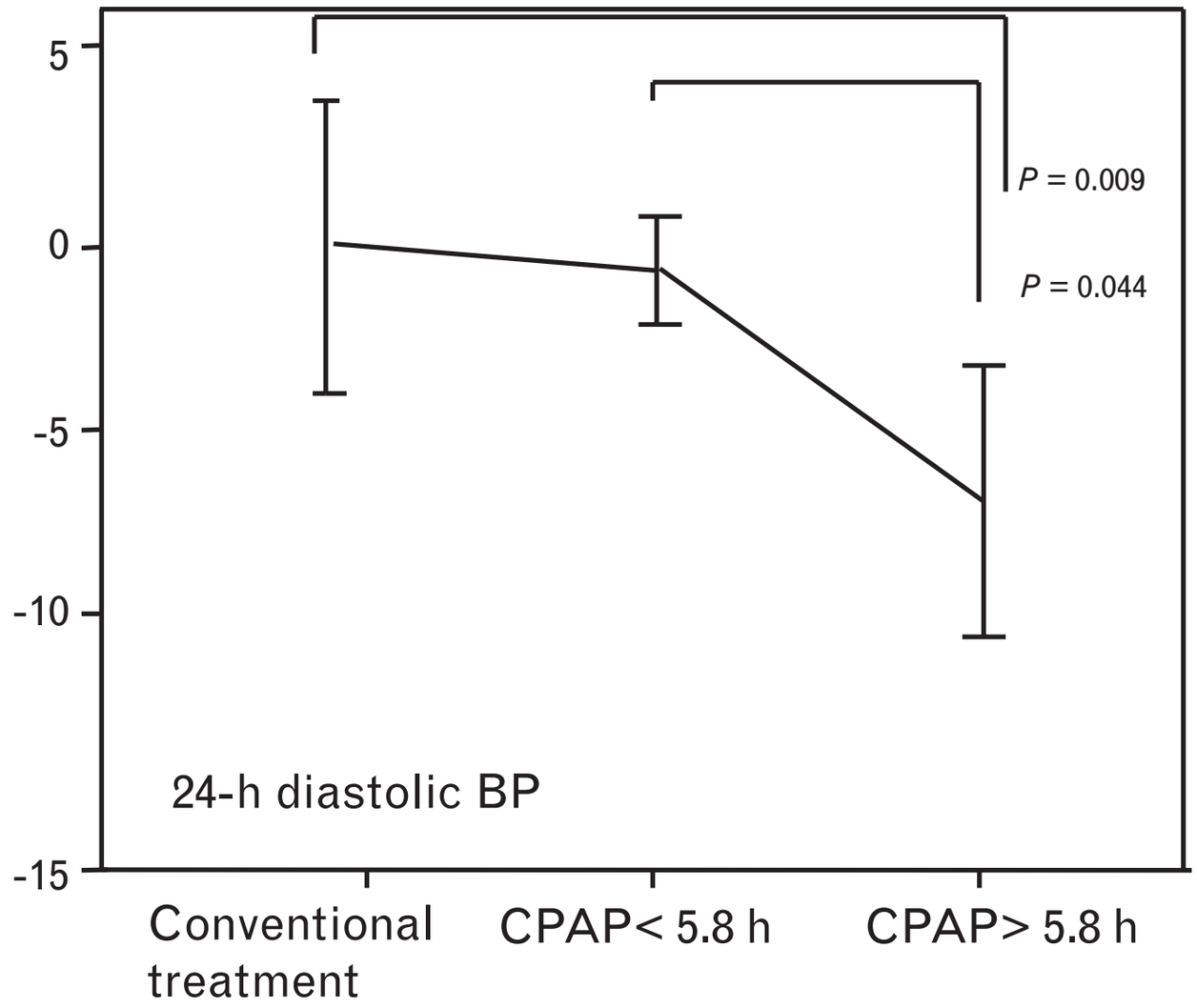
häufig

- ➡ Obstruktive Schlafapnoe 80%
- ➡ Niereninsuffizienz
- ➡ Primärer Hyperaldosteronismus 20% !
- ➡ Nierenarterienstenose 35%

selten

- ➡ Phäochromozytom 0,1-0,6%
- ➡ Cushing Syndrom
- ➡ Hyperparathyreodismus
- ➡ Aortenisthmusstenose
- ➡ Intracranielle Tumore


10
0
-10
-30
P = 0.046
P = 0.10
24-h systolic BP
Conventional treatment
CPAP< 5.8 h
CPAP> 5.8 h


5
0
-5
-10
-15
P = 0.009
P = 0.044
24-h diastolic BP
Conventional treatment
CPAP< 5.8 h
CPAP> 5.8 h

Resistant Hypertension or Resistant Prescribing?

Michael E. Ernst

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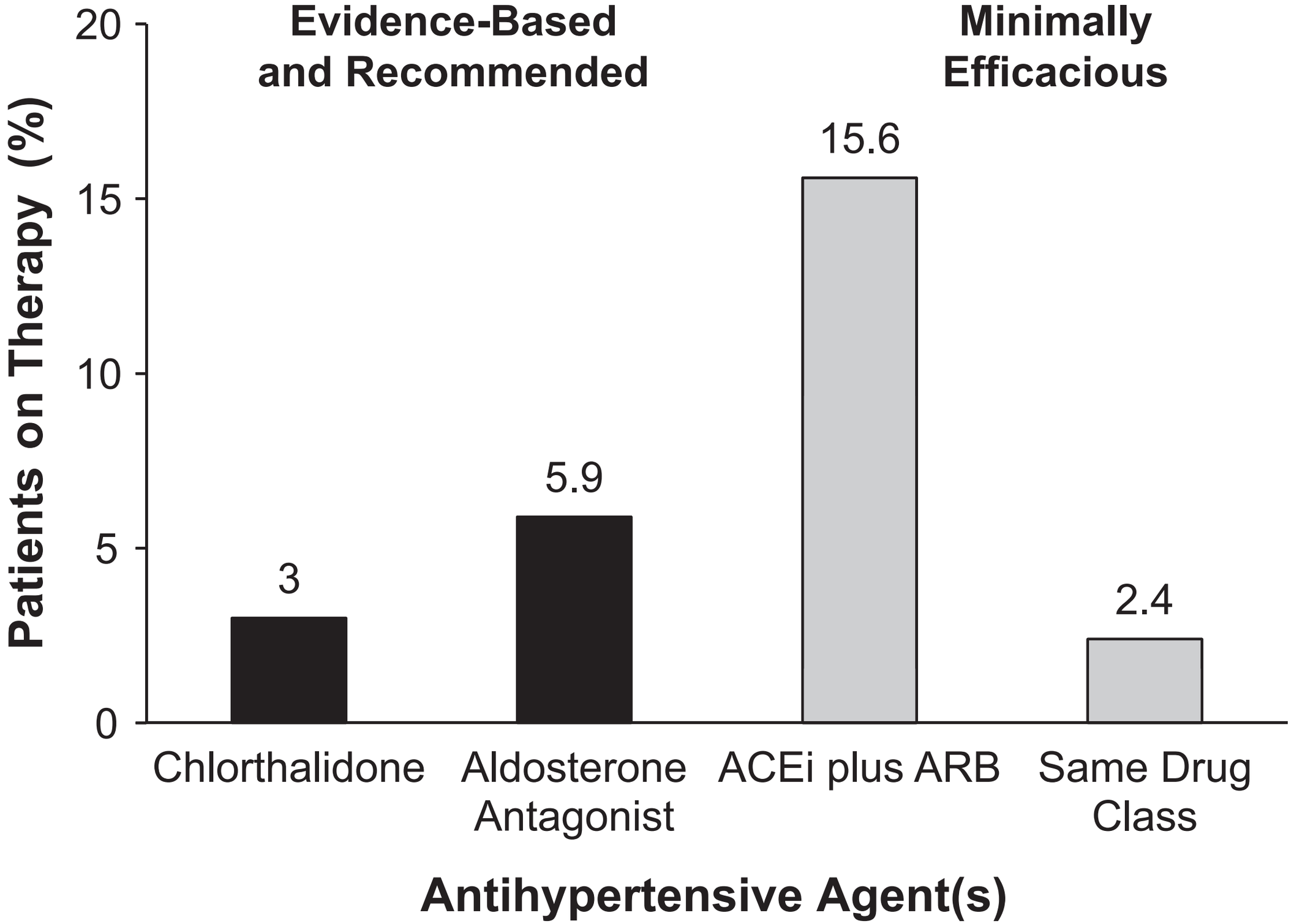
 Print ISSN: 0194-911X. Online ISSN: 1524-4563

Table 2. Antihypertensive Agents Used for the Treatment of Resistant Hypertension

Antihypertensive Medication Class	No. of Patients (N = 140 126)
ACEi	84 133 (60.0)
ARB	72 519 (51.8)
β-blocker	112 121 (80.0)
CCB	117 106 (83.6)
Dihydropyridine	97 655 (69.7)
Nondihydropyridine	21 069 (15.0)
Diuretic	130 629 (93.2)
Aldosterone antagonist	8212 (5.9)
Loop	26 375 (18.8)
Potassium sparing	1232 (<1.0)
Thiazide	111 758 (79.8)
α1-Adrenergic receptor antagonist	17 086 (12.2)
α2-Adrenergic receptor agonist	19 745 (14.1)
Direct renin inhibitor (aliskiren)	4706 (3.4)
Other	6529 (4.7)
Hydralazine	4443 (3.2)
Minoxidil	1712 (1.2)
Methyldopa	451 (<1.0)
Reserpine	30 (<1.0)


Evidence-Based and Recommended
Minimally Efficacious
Patients on Therapy (%)
20
15
10
5
0
3
5.9
15.6
2.4
Chlorthalidone
Aldosterone Antagonist
ACEi plus ARB
Same Drug Class
Antihypertensive Agent(s)

NSAIDs	Inhibition of PGE_2 and PGI_2 synthesis resulting in renal vasoconstriction, sodium, and water retention	Discontinue. If not possible, start calcium channel blockers or central adrenergic agonists, possibly associated with diuretics
Oral contraceptives and HRT	Increase in angiotensinogen synthesis, activation of RAS, aldosterone secretion, increase of plasma volume, and exchangeable sodium	In fertile women long acting calcium channel blockers, β-blockers, and methyldopa; consider diuretics. In postmenopausal women, also consider RAS inhibitors and aliskiren
HSD11B2 inhibitors Carbenoxolone Glycirrizinic acid Licorice	AME by inhibition of HSD11B2	Discontinue. If not possible, start MR antagonists.
Steroids	Increase in angiotensinogen synthesis, activation of the sympathetic nervous system, and mineralocorticoid effect	Discontinue. If not possible, start drugs blocking the RAS and the MR, along with adequate doses of diuretics to counteract sodium and water retention
Calcineurin inhibitors Cyclosporine Tacrolimus	Vasoconstriction, sympathetic activation and water and salt retention, impaired ET-1 clearance with enhanced ET_A effects.	Calcium channel blockers and RAS inhibitors
Erythropoietin	Rise of cytosolic Ca^{2+} content in vascular smooth muscle cells [67], activation of the local RAS system, increased ET-1 production, decreased NO, increased vasoconstricting response to catecholamines	Lower the dose; if unsuccessful, start calcium channel blockers or α-blockers. Diuretics and ACE inhibitors may be less effective
Sympathomimetic amines Cocaine Amphetamines Ephedrine Nasal decongestants	Cocaine and amphetamines: inhibition of the peripheral re-uptake ofNE and inhibition of baroreceptor function, thus causing sympathetic activation α-Adrenergic receptor stimulation	Discontinue offending drug if possible. If unfeasible, β-blockers
Alcohol	Stimulation of sympathetic activity, activation of the RAS, and abnormal calcium-mediated vasoconstriction	Limit intake
Caffeine	Sympathetic over-activation, antagonism of adenosine receptors, and increased norepinephrine release activation of the RAS system	Limit intake
Anti-angiogenesis and kinase inhibitors Bevacizumib RTKI	Blunted release of vasodilating factors, ET-1 stimulation, PGI_2 release, endothelial cell apoptosis, capillary rarefaction, and impaired angiogenesis of vasa vasorum with ensuing aortic stiffness	Drugs promoting NO bioavailability, such as ACE inhibitors and nebivolol
Antidepressants MAOIs Tricyclics Selective serotonin Re-uptake inhibitors (SSRI)	MAOI increase the half-life of monoamines as norepinephrine, thus enhancing their action at sympathetic nerve endings	Whenever withdrawal is unfeasible, use α-blockers with β-blockers
HDL-raising agents Torcetrapib	Increased aldosterone secretion	MR antagonists

NON-COMPLIANCE TO THERAPY AS A FREQUENT CAUSE OF RESISTANT HYPERTENSION – HOW COMMON AND HOW TO DETECT IT?

B. Strauch1, O. Petrak1, J. Rosa1, T. Zelinka1, Z. Somloova1, J. Kurcova2, L. Chytil2, R. Holaj1, J. Widimsky Jr1. 13rd Internal Clinic, General Teaching Hospital, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, 2Institute of Forensic Medicine and Toxicology, Toxicology Laboratory, General Teaching Hospital, 1st Faculty of Medicine, Prague, Czech Republic

.

.All patients underwent a clinical investigation including unplanned blood sampling for the measurement of concentration of several plasma antihypertensive drugs (amlodipin, betaxolol, bisoprolol, doxazosin, losartan, metoprolol, telmisartan, doxazosin, losartan, metoprolol..

In 40% of out-patients, the levels of antihypertensive drugs were non-detectable,

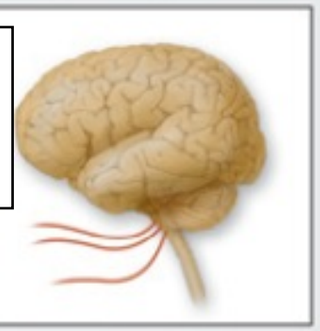
in next 40%, only levels of some of the prescribed drugs were positive and

in the rest 20% of patients plasma drug concentrations were within therapeutic limits. I

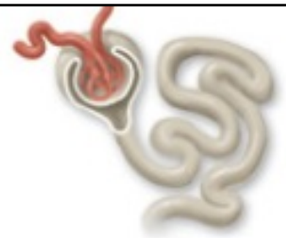
A

Salzreiche Kost

Erhöhte Sympathikus-aktivität



Störung der Natriumausscheidung



erhöhte Gefäßsteifigkeit

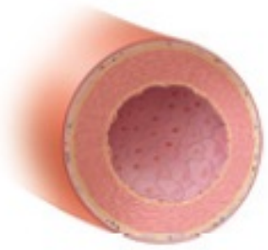
Aktivierung lokaler Angiotensin-systeme in Herz u.Gefässen

gesteigertes HZV

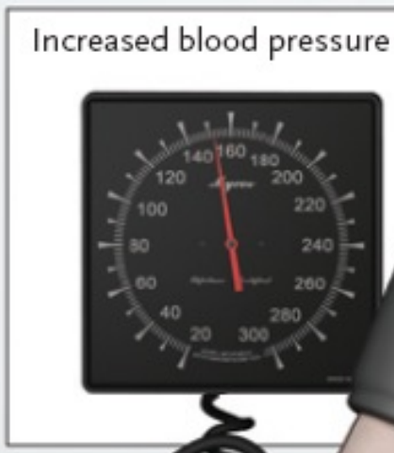
gesteigerte Natriumretention und Hypervolämie

RAAS-Stimulation in Niere und Nebenniere

erhöhter peripherer Widerstand, VSMC-Proliferation, endotheliale Dysfunktion



Haut: unphysiologische Salzspeicherung mit Induktion blutsteigernder Mediatoren



Wieviel Kochsalz braucht der Mensch?

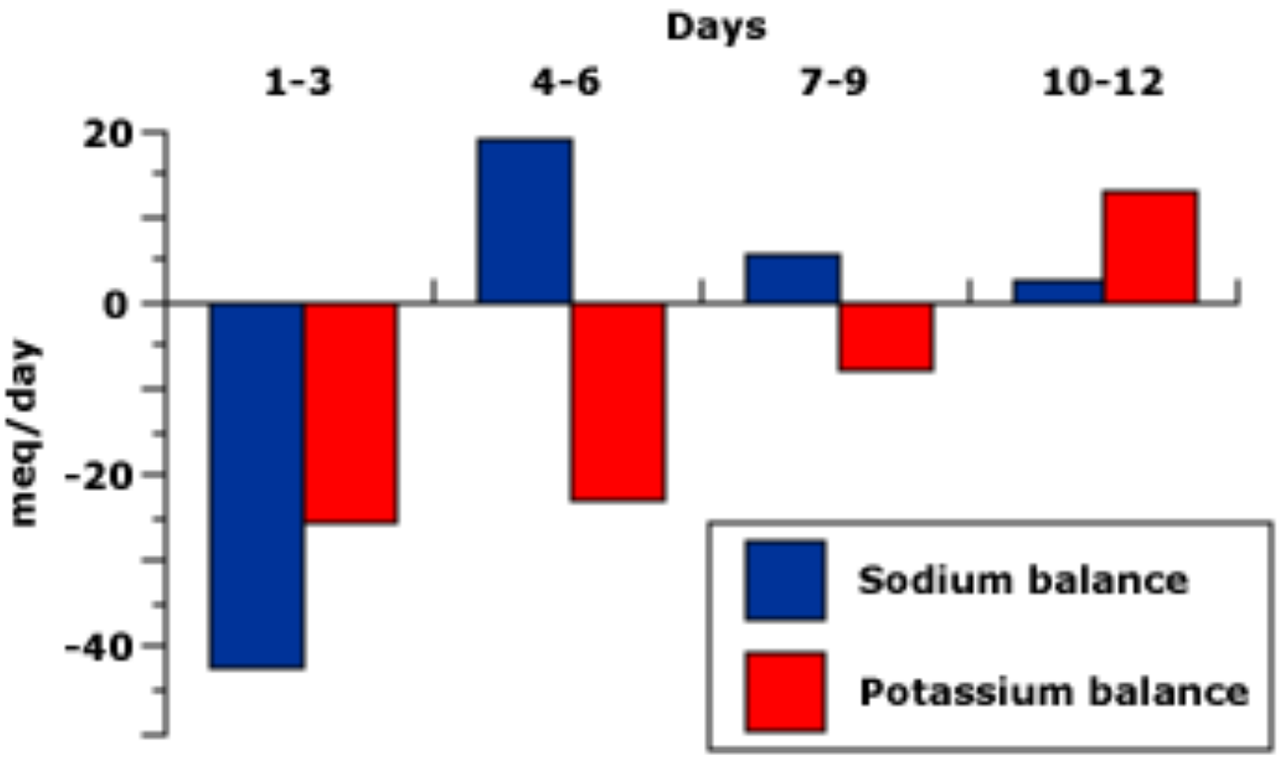
Eine Kochsalzufuhr <1g/Tag ist physiologisch gut möglich und verträglich

- unberührte Naturvölker:Yamamano (Brasilien)
- Völker, bei denen es natürliche Möglichkeiten zur Konservierung gab: , z.B. Eskimo
- Menschen in Umwelten ohne Salz: z.B. nomadische Tuareg

REALITÄT DER KOCHSALZZUFUHR
INTERSALT STUDIE

- 10.079 Probanden aus 52 Ländern
- repräsentative Normalbevölkerung
- Natriumauscheidung i.U. 170 mmol/Tag
- entspricht ca. 9 g Natriumchlorid /Tag

Steady state after thiazide therapy



Data from Maronde, RF, Milgrom, M, Vlachakis, ND, Chan, L, JAMA 1983; 249:237.

Therapie

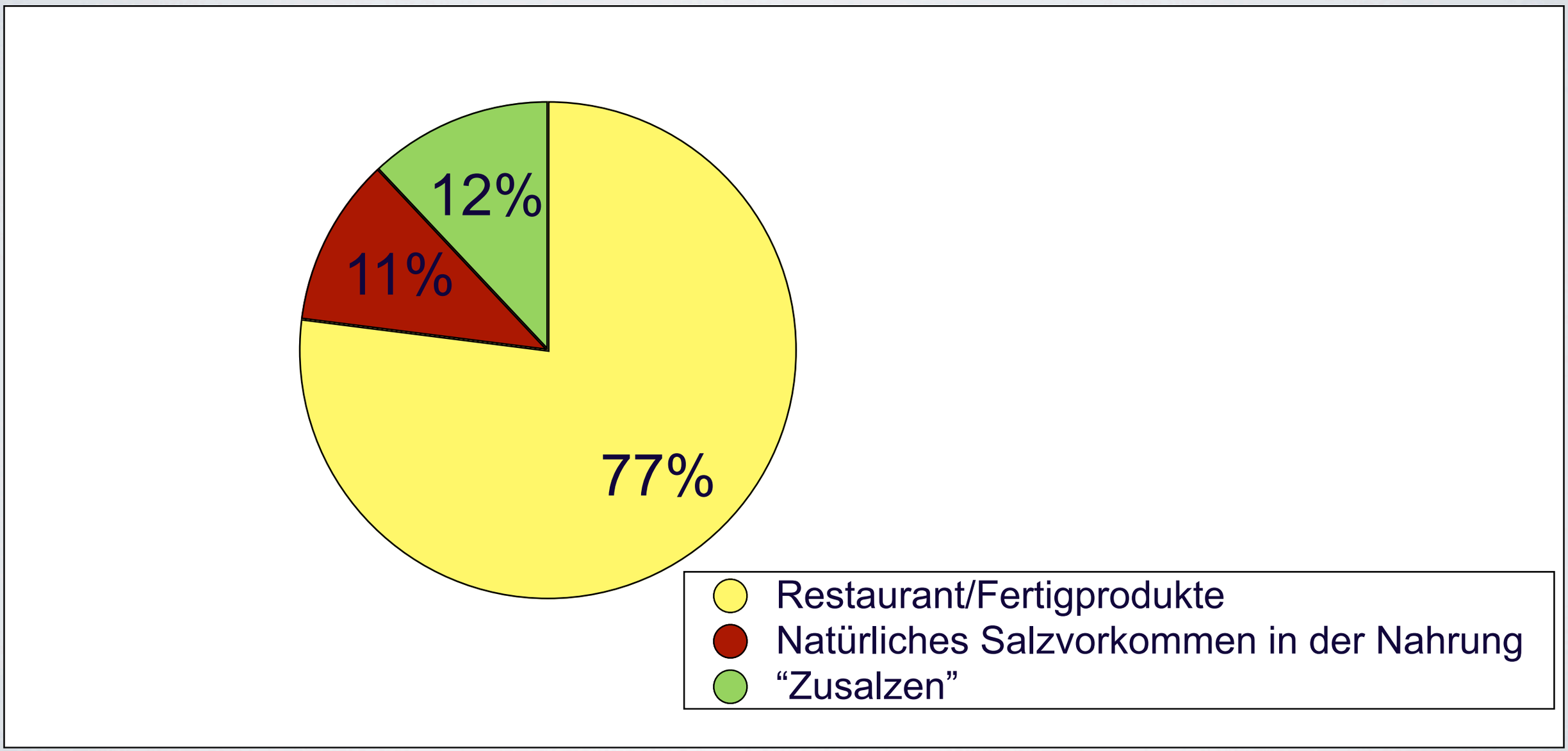
Nicht Pharmakologisch

Lifestyle

Pharmakologisch

Andere

HERKUNFT DES KOCHSALZ IN DER NORMALEN NAHRUNG



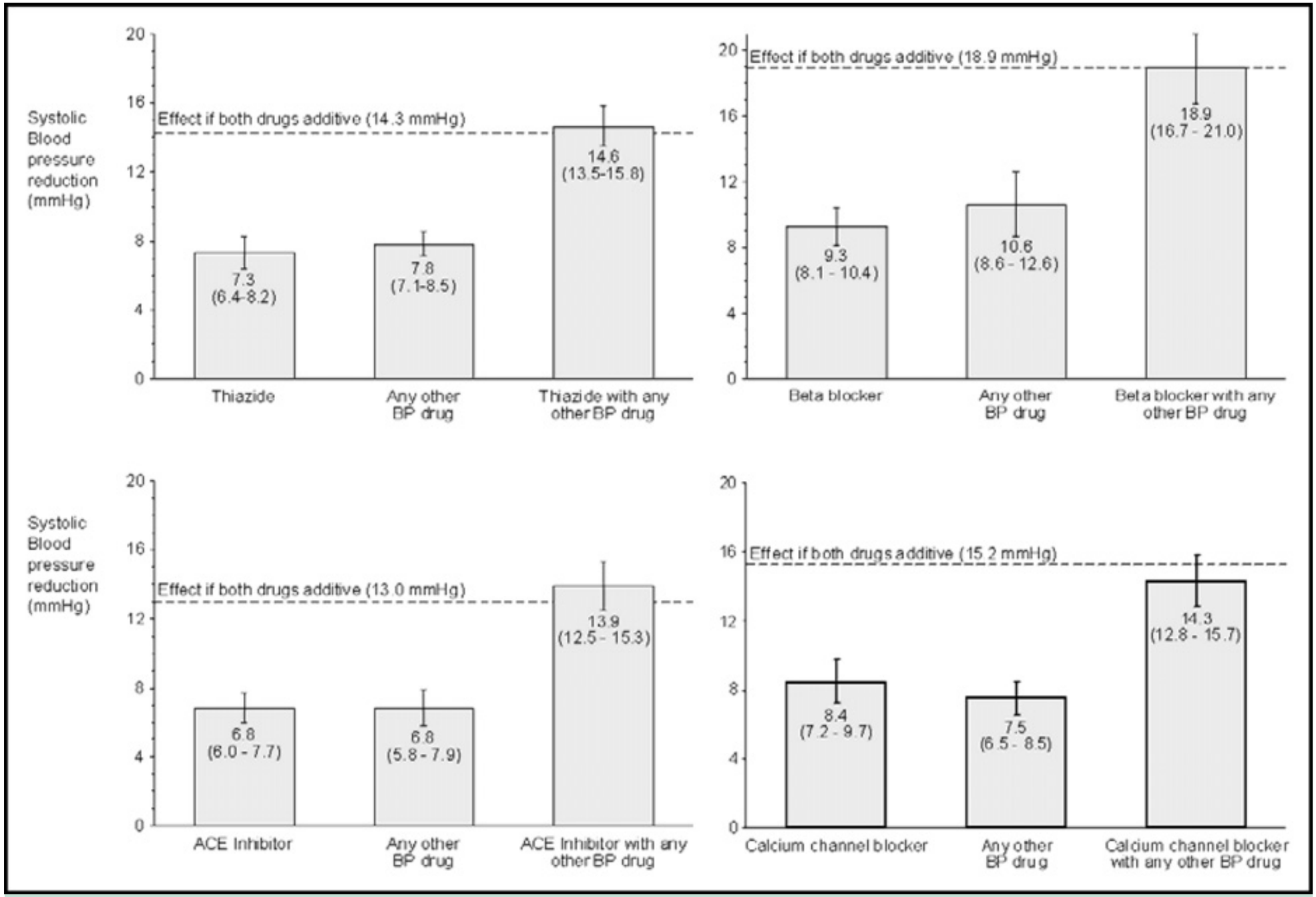
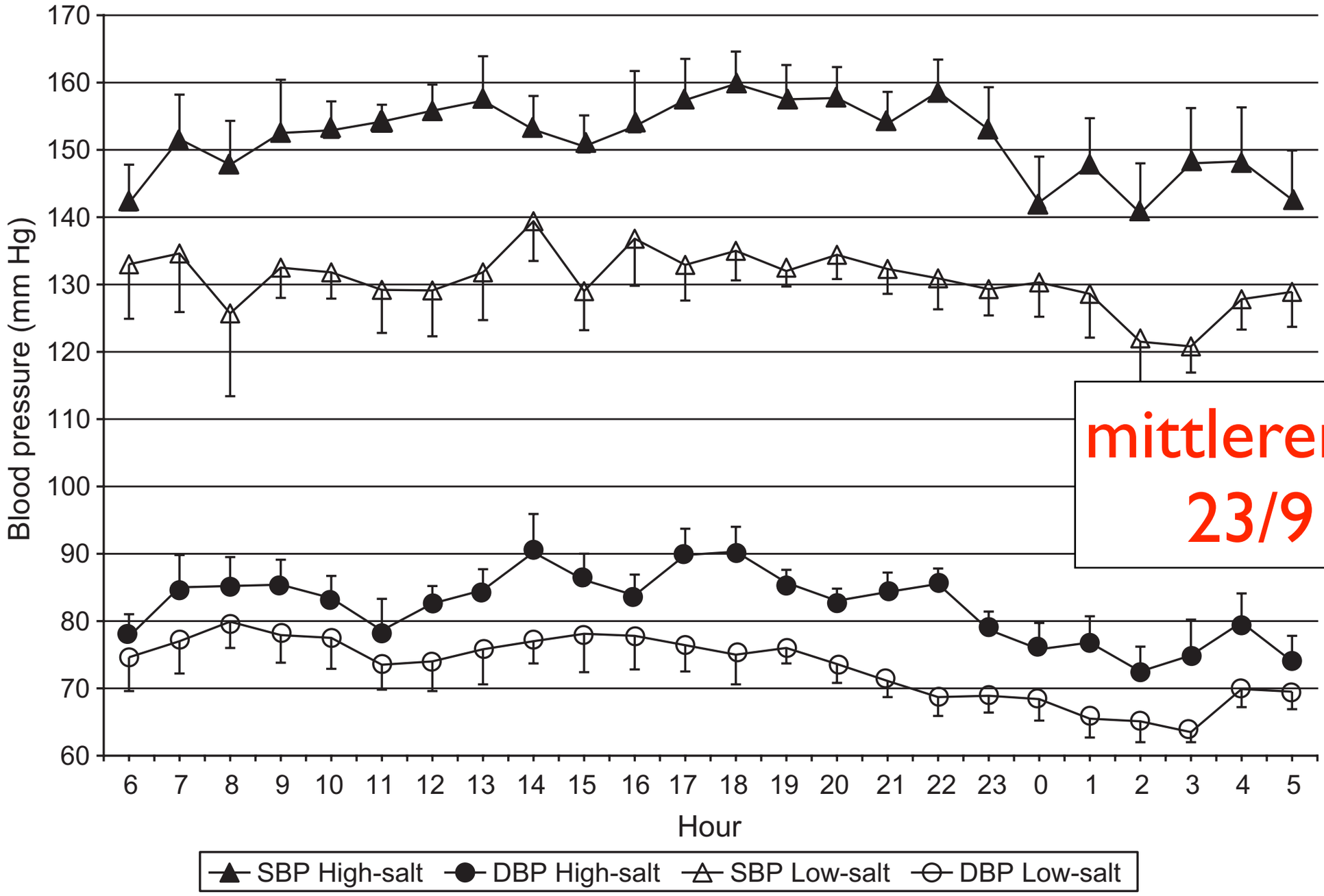


Figure 1 Mean placebo-subtracted systolic blood pressure reduction from a meta-analysis of 42 randomized factorial trials of thiazides, beta-blockers, ACE inhibitors, or calcium channel blockers using each class of drug separately, any 1 of the other 3 classes alone, and in combination with the specified drug class (95% confidence interval). The dashed line represents the expected blood pressure reduction from the combination assuming an additive effect, allowing for the smaller reduction from 1 drug given the lower pretreatment blood pressure because of the other. BP = blood pressure; ACE = angiotensin-converting enzyme.



mittlerer RR Abfall
23/9 mmHg

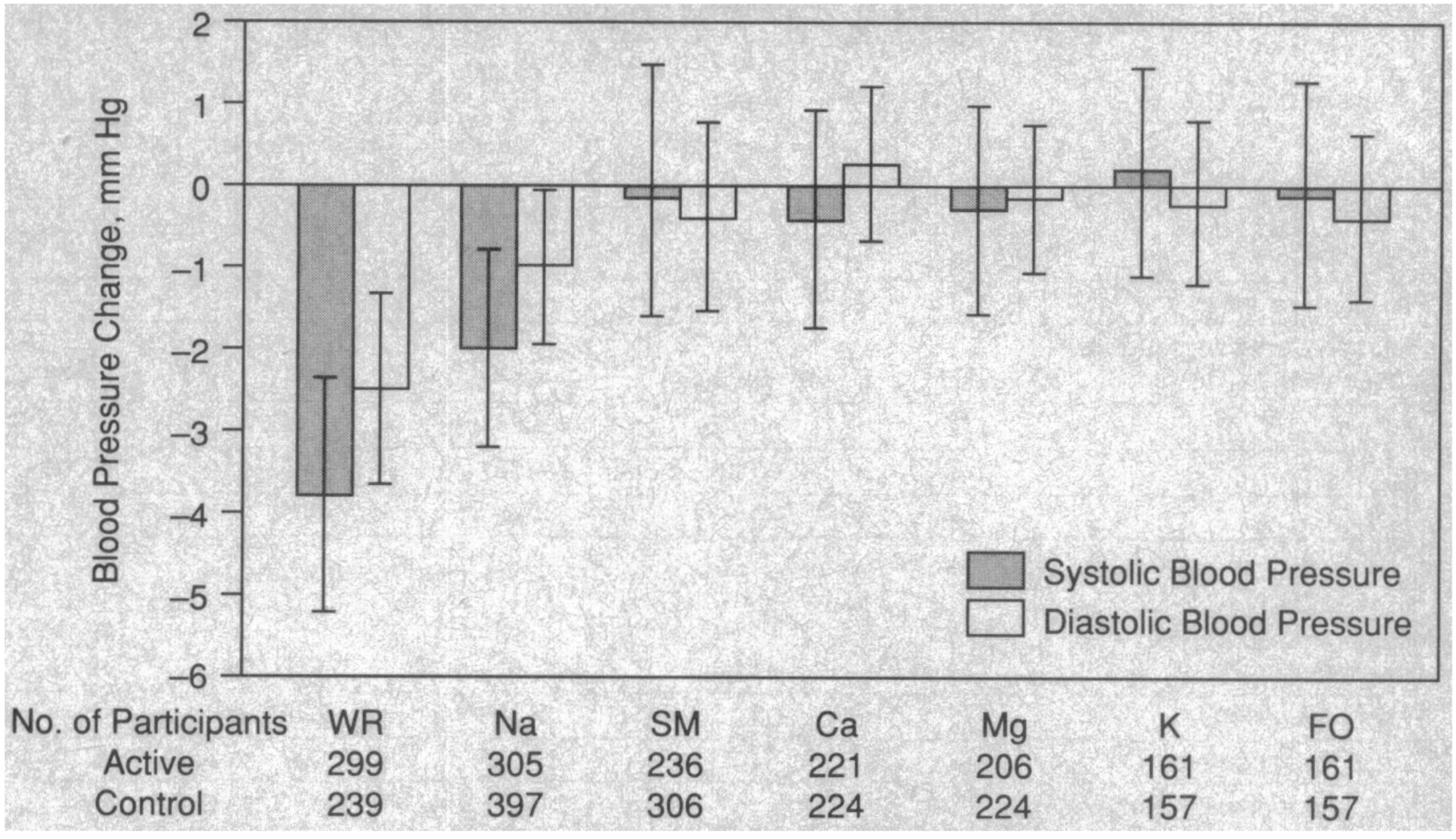
. Comparison of 24-hour ambulatory blood pressure values during low- and high-salt diet. Data presented as mean±SE.

Salzrestriktion bei resistenter Hypertonie

EMPFEHLUNGEN DER FACHGESELLSCHAFTEN ZUR KOCHSALZREDUKTION

- < 6(5) g Kochsalz /Tag
- European Society of Hypertension
- DHL/Deutsche Hypertoniegesellschaft
- AHA/ American Society of Hypertension
- Canadian Hypertension Society
- (World Health Organization)

Nicht Pharmakologisch



No. of Participants	WR	Na	SM	Ca	Mg	K	FO
Active	299	305	236	221	206	161	161
Control	239	397	306	224	224	157	157

Fig 2.—Net mean changes in systolic and diastolic blood pressure (baseline minus follow-up), with 95% confidence intervals. WR indicates weight reduction; Na, sodium reduction; SM, stress management; Ca, calcium supplementation; Mg, magnesium supplementation; K, potassium supplementation; and FO, fish oil supplementation.

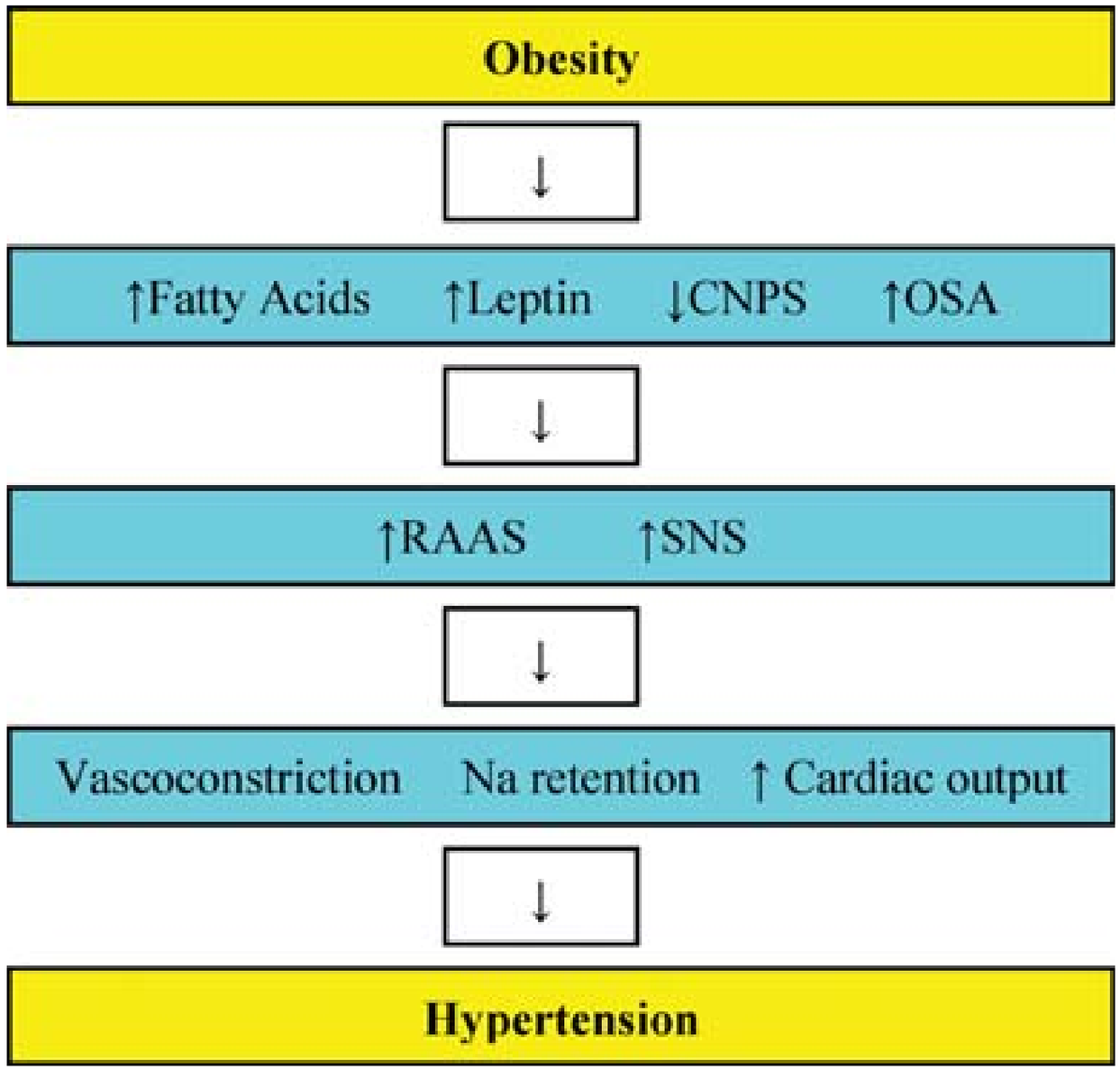


Figure 1 Hypothetical mechanisms by which obesity may contribute to HTN. CNPS, cardiac natriuretic peptide system; OSA, obstructive sleep apnoea; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system.

Does it matter how one loses the weight?

The short answer is yes. Among the possible means of reducing body weight are lifestyle modifications, pharmacological interventions, and invasive or surgical interventions.

A 4 kg weight loss achieved with dietary treatment yielded a 6 mmHg systolic BP (SBP) reduction; the same 4 kg weight loss achieved with orlistat (decreases dietary fat absorption by inhibiting activity of pancreatic lipases) yields a lesser 2.5 mmHg reduction in SBP.[16] An 8.4 kg reduction in weight using orlistat yielded a 4.0/3.0 mmHg reduction in BP, whereas an 8.3 kg weight reduction through the use of sibutramine (serotonin–norepinephrine reuptake inhibitor that acts as an appetite suppressant) did not cause a change in BP. Sibutramine may actually have a BP-raising effect that counteracts the BP reduction that comes with its weight loss effects. In the SCOUT trial, sibutramine was associated with a higher composite risk of heart attack, stroke, resuscitated cardiac arrest, or death.[17]

Macht es einen Unterschied wie man abnimmt?

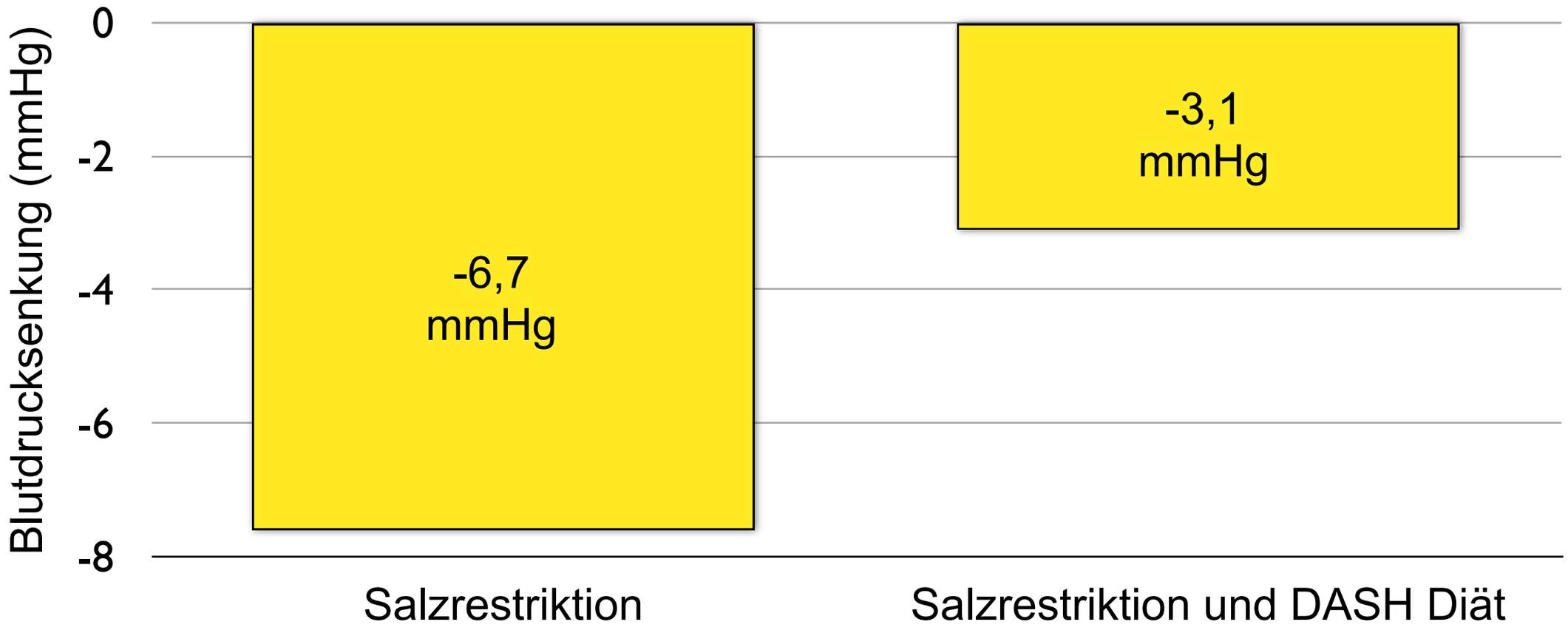
- Ja
- -4 kg durch Diät -> -6,0 mmHg systolisch
- -4 kg durch Orlistat -> -2,5 mmHg systolisch
- -8 kg durch Orlistat -> -4,0 mmHg systolisch
- -8 kg durch Sibutramin ?

Macht es einen Unterschied wie man abnimmt?

- Ja
- -4 kg durch Diät -> -6,0 mmHg systolisch
- -4 kg durch Orlistat -> -2,5 mmHg systolisch
- -8 kg durch Orlistat -> -4,0 mmHg systolisch
- -8 kg durch Sibutramin ? kein Effekt !

Nicht Pharmakologisch

Lifestyle



HYPERTONIE MECHANISMEN

- Volumen
- Renin Angiotensin System
- Sympathikusaktivierung

3 Tabletten Regime*

Anti-Volumen+ (Anti-RAS+X)

Option A:
Diuretikum optimieren

Option B:
Sympathikus behandeln

Option C:
(..X) optimieren

Option A + Option B + Option C

Hydrazalin oder zentraler Alfa-Agonist

Sympathikusablation □

Option A:
Diuretikum optimieren*

- hoher Salzverzehr
- Ödeme
- Niereninsuffizienz (GFR <30 ml/min?)
- niedriger Reninspiegel
- normale Harnstoff/Harnsäurespiegel

nur 30% der Patienten mit einer GFR <30 ml/min erhalten ein Schleifendiuretikum

Option A:
Diuretikum optimieren*

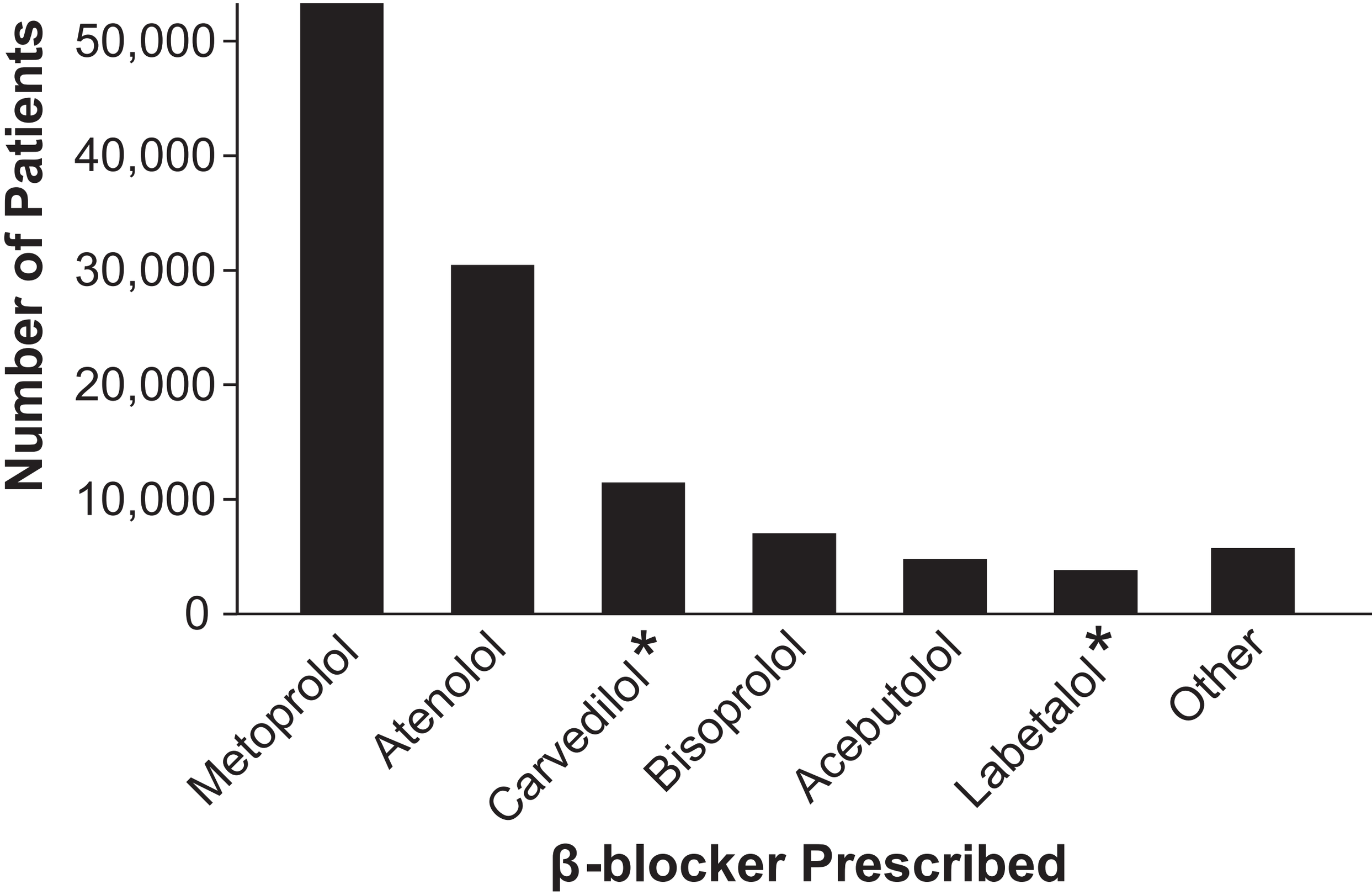
- Wechsel auf Chlorthalidon 25 mg
- zusätzlich Epleneron/Spironolacton/ Amilorid
- Wechsel auf ein Schleifendiuretikum
- sequentielle Nephronblockade

Option B:
Sympathikus behandeln

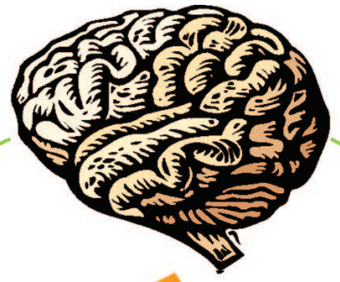
- Schlafapnoe
- Akuter/Z.n. Schlaganfall
- C2 Abusus
- Hypertonie mit Sinustachkardie
- Paroxysmale Hypertonie

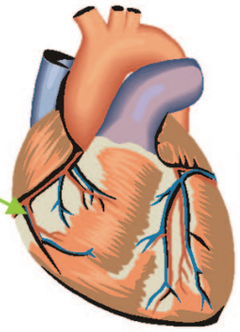
Option B:
Sympathikus behandeln

- kombinierte Alfa/Betablockade
- Herzfrequenz sollte sinken
- Renin sollte supprimert werden
- in Kombination mit ACEi/ BB reichen oft niedrigere Dosen Alphablocker
- Bisoprolol/ Nebivolol am besten


Number of Patients
50,000
40,000
30,000
20,000
10,000
0
Metoprolol
Atenolol
Carvedilol*
Bisoprolol
Acebutolol
Labetalol*
Other
β-blocker Prescribed

Smooth Muscle -
Migration
Vasoconstriction
Atherosclerosis

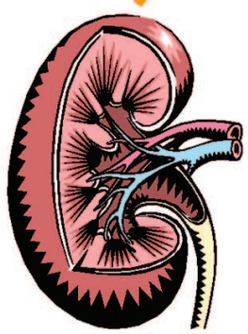




Hypertrophy
Arrhythmias
Ischemia
Heart Failure

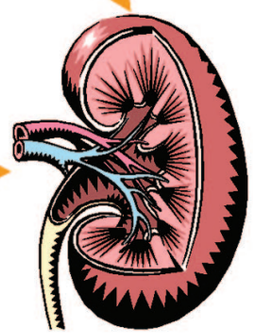
Renal Afferent Nerves

Renal Efferent Nerves



Renal ischemia
↓Stroke Volume
↑Adenosine

Renal Afferent Nerves



Renin Release
- RAAS
- Systemic Sym Gain

Sodium Retention
- Hypervolemia
- Wall stiffness

Decreased RBF
Proteinuria
BNP Resistance

Sympathikusaktivierung

- Steigerung der Reninsekretion (ß1)
- Natrium- und Wasserretention (α1B)
- Renale Vasokonstriktion (α1A)
- graduierte Effekte

Radiofrequency ablation of sympathetic fibers

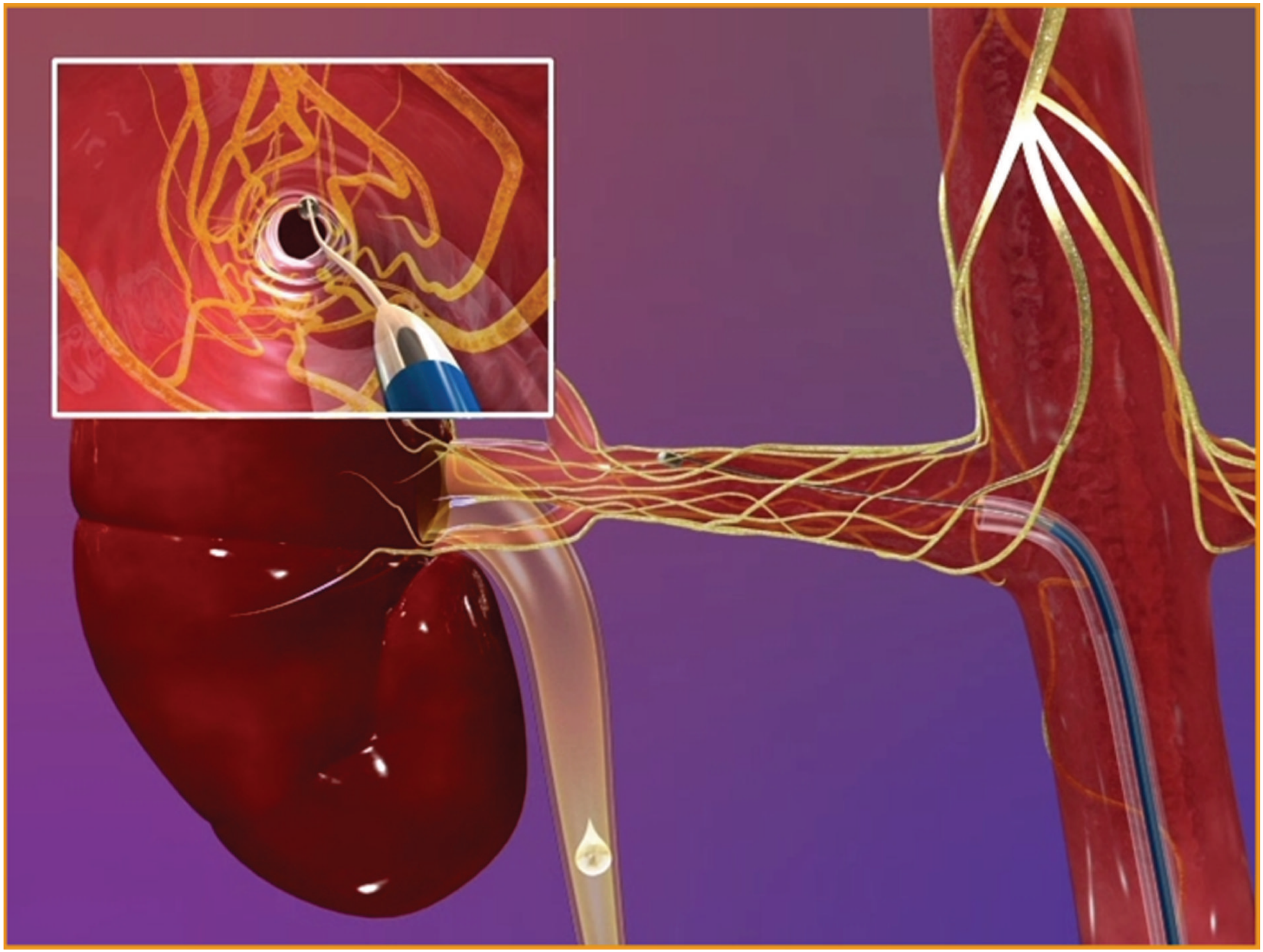
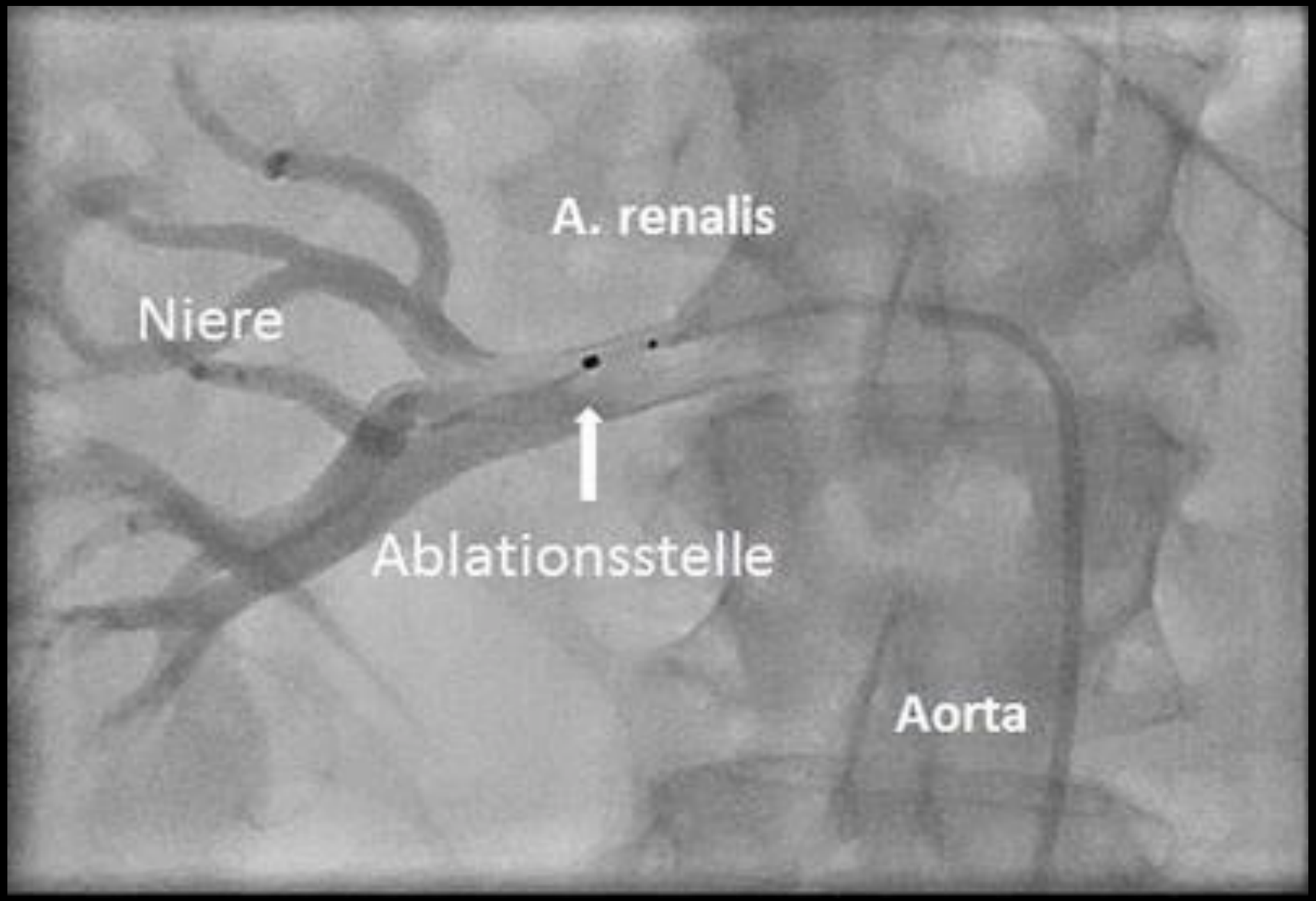


Figure 4: Sympathetic fibers, both efferent and afferent, are found in the adventitia of renal arteries. These fibers can be ablated using specialized catheters that deliver radiofrequency energy.


A. renalis
Niere
Ablationsstelle
Aorta

Denervierung
Wirkmechanismus 1

Efferente Denervierung

- Renin-Angiotensin-Aldosteron reduzieren
- renalen Gefässwiderstand senken, GFR und RBF erhöhen
- Natriumresorption - und retention reduzieren

- aber: efferente Nerven wachsen nach
- anatomische oder funktionelle Reinervation

->RR Effekt bleibt!!!

Denervierung Wirkmechanismus 2

Afferente Denervierung

- afferente Stimulation ins ZNS reduzieren
- normale Niere: inhibitorischer Input aus pelvinen Mechanorezeptoren
- „kranke“Niere: exzitatorischer Input aus renalen interstitiellen Chemorezeptoren

- wachsen afferente Nerven nach? keine direkten Daten
- Bespiel Herztransplantation, nach 5 Jahren nicht

Tests??

STUDIEN ZUR SYMPATHIKUSABLATION

- n = 45, feasibility, nicht randomisiert
- n = 153, HTN 1, open label, randomisiert
- n = 106, HTN 2, randomisiert kontrolliert
- n = 530, US Multicenter Studie randomisiert , doppel blind mit Sham Denervation läuft -> 2016

Simplicity
Proof of concept

- 5 RR Medis (Abb 2, Hypertension 5/2011)
- mittlere GFR 83 ml/min
- 1° Endpunkt: Office RR sys nach 6 Monaten

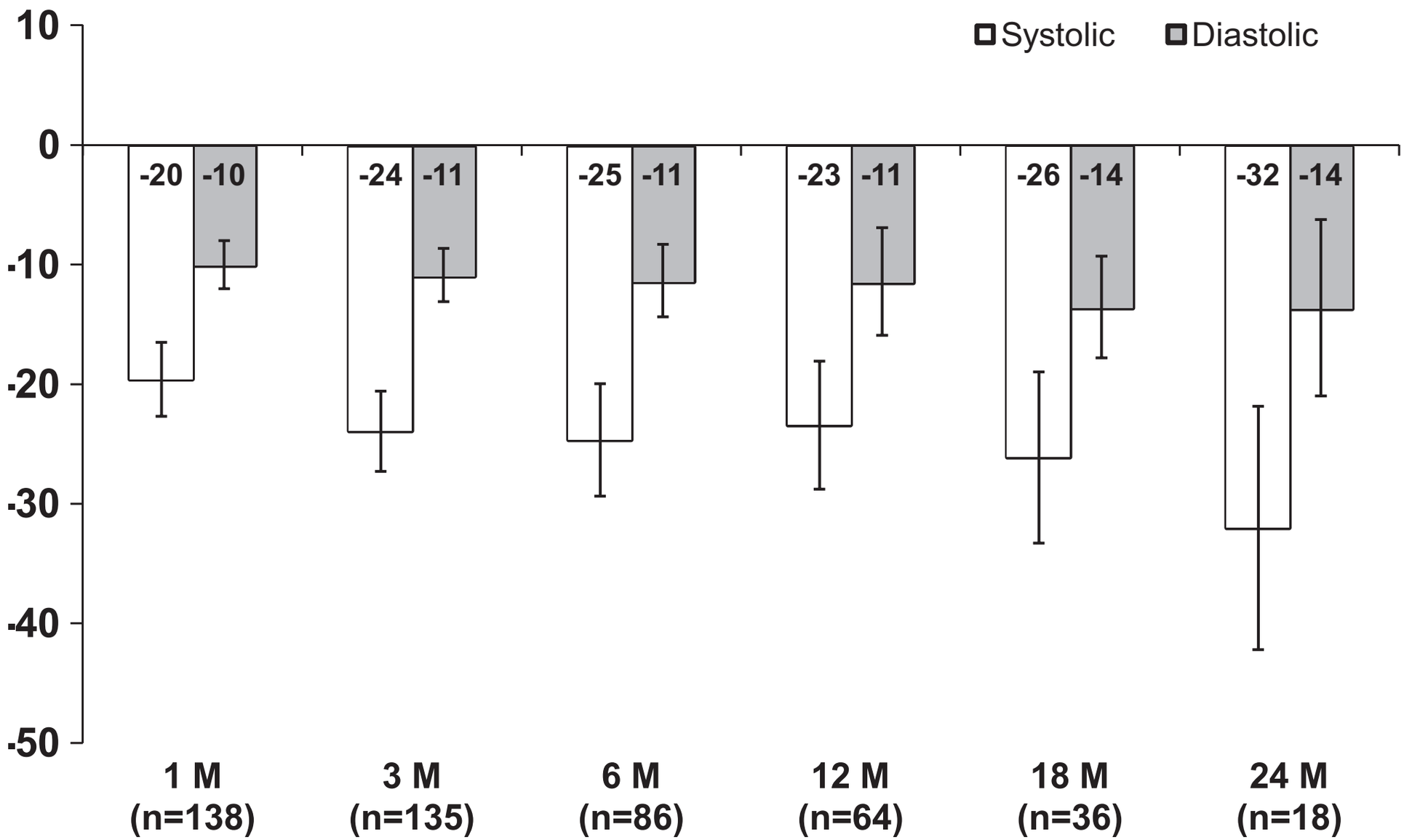
Simplicity
Proof of concept

- Sek Endpunkte: akute und chronische Sicherheit der Prozedur
- GFR Abfall >25%
- de novo Nierenarterienstenose > 60%, angiografisch bestätigt
- Kombinierter Endpunkt zur kardiovaskulären Ereignissen

Stärken

- Einschluß erst, wenn 2x RR (20% so ausgeschlossen)
- RR Gerät und Medlogs
- →Ausschluß Hawthorne Effekt und Regression zum Mittelwert
- RR Kontrolle mittels ABDM reduziert Interobserver Variabilität

24 Monatsdaten
Änderung der Praxisblutdrucks versus Baseline



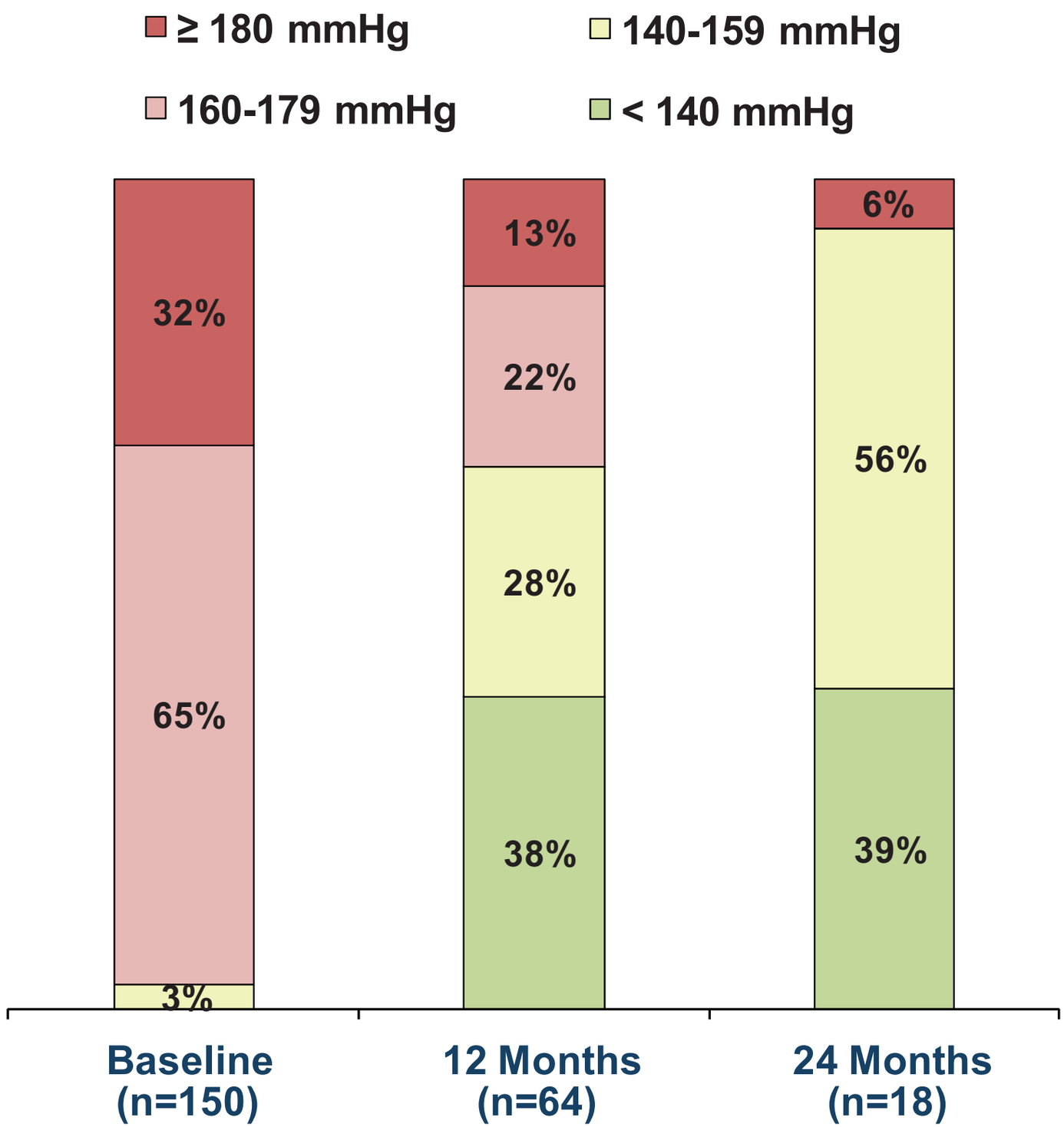
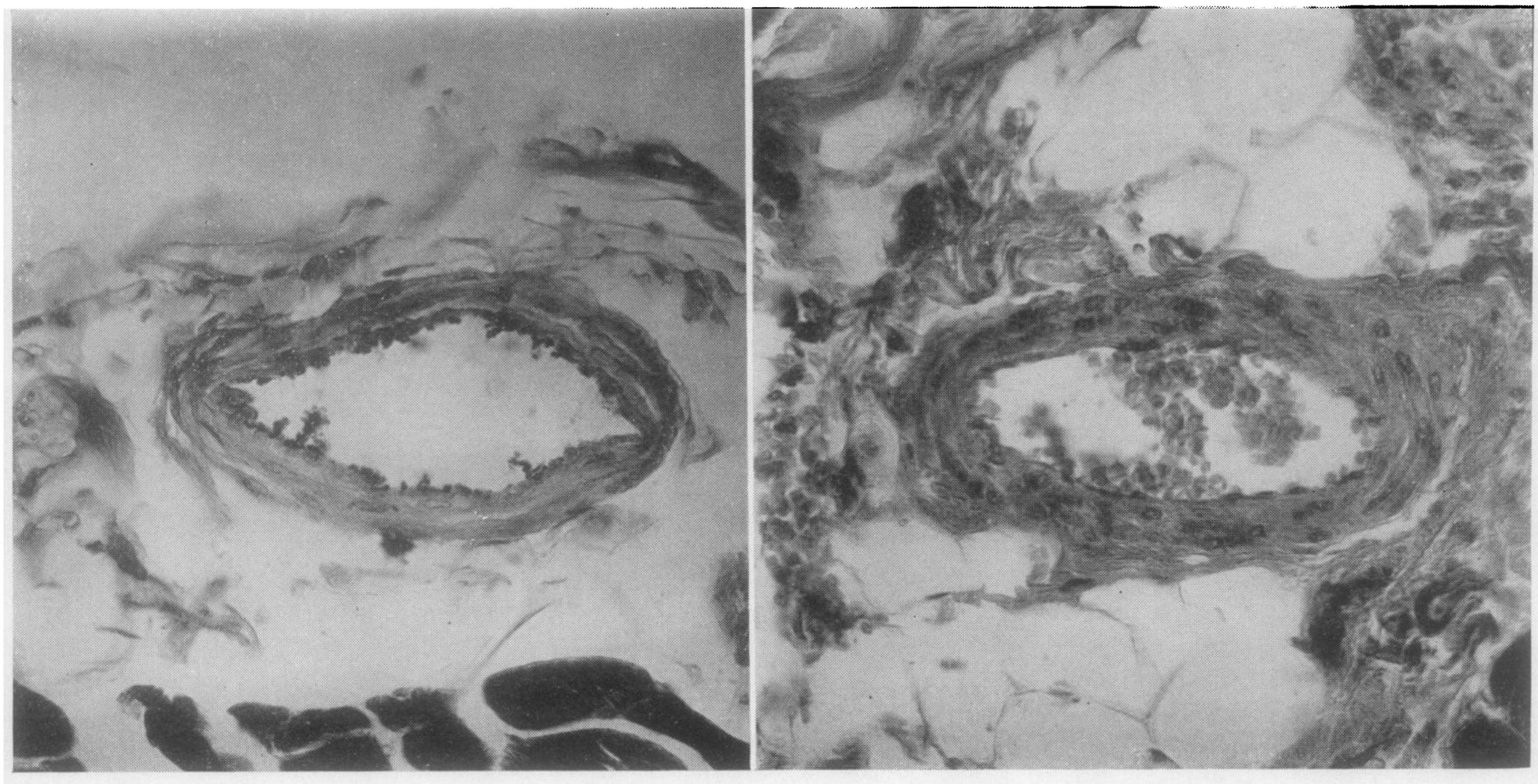


Figure 2. Distribution of office systolic BP in patients at baseline, 12 months, and 24 months.

Sympathikusablation



1.

Section of Artery of Normal Man 40 Yrs. Old.
× 450.

2.

Section of Patient's Artery.
× 500.

Ergebnisse 2
Nebenwirkungen

- 97% keine (149/153)
- Schmerzen
- Bradykardie
- 1 Nierenarteriendissektion (Stent; bei Katheterplazierung, vor Ablation)
- Pseudoaneurysma/Leistenhämatom

Schwächen

- Sample size zu gering
- Follow up zu kurz für harte Endpunkte
- keine Sham Denervation
- keine Verblindung
- RR Senkung ABDM nur 1/3 des Office RR
- kein Ausschluss sekundärer Bluthochdruckformen

Randomised controlled trial

Catheter-based renal sympathetic denervation reduces systolic blood pressure by 32 mm Hg in people with treatment-resistant hypertension

Richard E Katholi,[1] **Krishna J Rocha-Singh**[1]

Commentary on: **Esler MD**, Krum H, Sobotka PA, *et al.*; Symplicity HTN-2 Investigators. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010;**376**:1903–9.

Commentary

This randomised trial adds support to the non-randomised preliminary study indicating that catheter-based renal sympathetic denervation in patients with resistant essential hypertension is safe and lowers systolic blood pressure by 27–32 mm Hg, whereas the eGFR remains stable.[3] As other factors (renin–angiotensin–aldosterone system, sodium, volume and vascular hypertrophy) contribute to the maintenance of hypertension, most of these patients will continue to require antihypertensive therapy. Of note, 16% of patients who underwent catheter-based renal den-

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Renal Sympathetic Denervation: Renal Function Concerns

Konstantinos Petidis, Panagiota Anyfanti and Michael Doumas

Hypertension 2011, 58:e19: originally published online August 22, 2011
doi: 10.1161/HYPERTENSIONAHA.111.178145
Hypertension is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0194-911X. Online ISSN: 1524-4563

Ergebnisse Nierenfunktion

- nach 1 Jahr +0,1 bis - 2,9 ml/min (n=102)
- nach 2 Jahren (n= 10!)
- → -16 ml/min (neues Diuretikum)
- → -7,8 ml/min (3,9 ml/min/Jahr)

Take home message

Therapieresistenz bestätigen

Pseudoresistenz ausschliessen

Lifestyle/Medikation optimieren

Hypertoniespezialist

Sympathikusablation erwägen

Follow up-> Nierenfunktion

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Is It Ethical to Perform Irreversible Renal Denervation Before a Trial of Low Sodium Intake for Treatment-Resistant Hypertension?

Martin J. Turner and Johan M. van Schalkwyk

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doi: 10.1161/HYPERTENSIONAHA.111.176297
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 Print ISSN: 0194-911X. Online ISSN: 1524-4563

Sollen übergewichte Patienten, die zuviel Kochsalz essen eine Sympathikusablation erhalten???

Table 1 Baseline Characteristics

	All Patients (N = 46)	Renal Denervation (n = 37)	Control Group (n = 9)	p Value*
Age, yrs	60.2 ± 9.1	59.1 ± 9.4	64.9 ± 6.4	0.087
Male	32 (70%)	25 (68%)	7 (79%)	0.561
Resting SBP, mm Hg	171 ± 24	172 ± 24	166 ± 23	0.507
Resting DBP, mm Hg	93 ± 18	94 ± 19	90 ± 7	0.579
Heart rate at rest, beats/min	73 ± 13	73 ± 14	74 ± 9	0.282
eGFR, ml/min/1.73 m^2	69 ± 23	70 ± 24	64.5 ± 16	0.510
BMI, kg/m^2	31.5 ± 5.1	31.8 ± 5.2	30.2 ± 4.6	0.391
Type 2 diabetes	18 (39%)	16 (43%)	2 (22%)	0.247
Coronary artery disease	7 (15%)	4 (11%)	3 (33%)	0.092
Hypercholesterolemia	29 (63%)	21 (57%)	8 (89%)	0.073
Number of antihypertensive drugs	5.7 ± 1.4	5.9 ± 1.4	5.0 ± 1.2	0.119
Patients receiving, drug class				
ACE inhibitors/ARBs	42 (91%)	33 (89%)	9 (100%)	0.302
Direct renin inhibitors	13 (28%)	10 (27%)	3 (33%)	0.499
Beta-blockers	42 (91%)	33 (89%)	9 (100%)	0.405
Calcium-channel blockers	37 (80%)	31 (84%)	6 (67%)	0.427
Diuretics	40 (87%)	33 (89%)	7 (78%)	0.642
Sympatholytics	26 (57%)	22 (60%)	4 (44%)	0.328

ERGEBNISSE 2
NEBENWIRKUNGEN

Substanz	Markenname	Pro-Drug	aktive Substanz	Bioverfügbarkeit nach oraler Gabe in % (M)	Proteinbindung in %	Elimination **	Qo (M)	t_{max} (h)	t1/2 (h)
kurze Halbwertszeiten (2–8 h)									
Captopril	Lopirin/ Tensobon	nein	Catopril	70	30	R	0,4	1,0	2,0
Cilazapril	Inhibace	ja	Cilazaprilat	45–75	<50	R	(0,2)	1,0–2,0	1,0–2.0
Quinapril	Accupro	ja	Quinaprilat	60	97	R	0,6 (0,2)	1,0–2,0	3,0
mittlere Halbwertszeiten (9–14 h)									
Benazepril	Cibacen	ja	Benazeprilat	28–37	92–96	R/H	1,0 (0,2)	1,5	11,0
Enalapril	Reniten	ja	Enalaprilat	40–60 (40)	<50	R	(0,6)	3,0–4,0	11,0
Fosinopril	Fositen	ja	Fosinoprilat	25–29	95	R/H 50:50	0,9	3,0	12,0
Lisinopril	Zestril/Prinil	nein	Lisinopril	25	3–10	R	0,2	6,0–7,0	10–13
Perindopril	Coversum	ja	Perindoprilat	75 (20)	10–20	R	0,25	2,0–6,0	7,0–9,0
Ramipril	Triatec/Vesdil	ja	Ramiprilat	30 (56)	56–73	R/H 70:30	1,0 (0,2)	2,0–3,0	10–16
lange Halbwertszeiten (>20 h)									
Spiralpril	Cardiopril	ja	Spiraprilat	40–50	86–91	R/H 50:50	?	2,5	30,0
Trandolapril	Gopten	ja	Trandolaprilat	11	80–94	R/H 30:70	?	4,0–8,0	16–24

(M): pharmakologisch aktive Metabolite; **: Ausscheidung in %; renal-R, heptisch-H; Qo: extrarenal (nicht renal) eliminierte Dosis-Fraktion; t_{max}: Dauer bis zum Erreichen der Plamaspitzenkonzentration in Stunden; t1/2: Eliminationshalbwertszeit in Stunden

PATIENTENCHARAKTERISTIKA

- Alter, weiblich
- Diabetes Mellitus
- Übergewicht
- Chronische Niereninsuffizienz
- Hoher Salzkonsum
- linksventrikuläre Hypertrophie

- # Renal artery diameter, renal function and resistant hypertension in patients with low-to-moderate renal artery stenosis

Zanoli, Luca; Rastelli, Stefania; Marcantoni, Carmelita; Tamburino, Corrado; Laurent, Stephane; Boutouyrie, Pierre; Castellino, Pietro

Abstract

Background: Atherosclerotic renovascular disease is associated with resistant hypertension and chronic kidney disease, although the causal relationship is discussed. To date, the role of renal artery diameter on these pathological conditions was not clearly studied. We aimed to identify the association of reference diameter and minimal luminal renal artery diameter with glomerular filtration rate (GFR) and resistant hypertension in a high cardiovascular risk population.

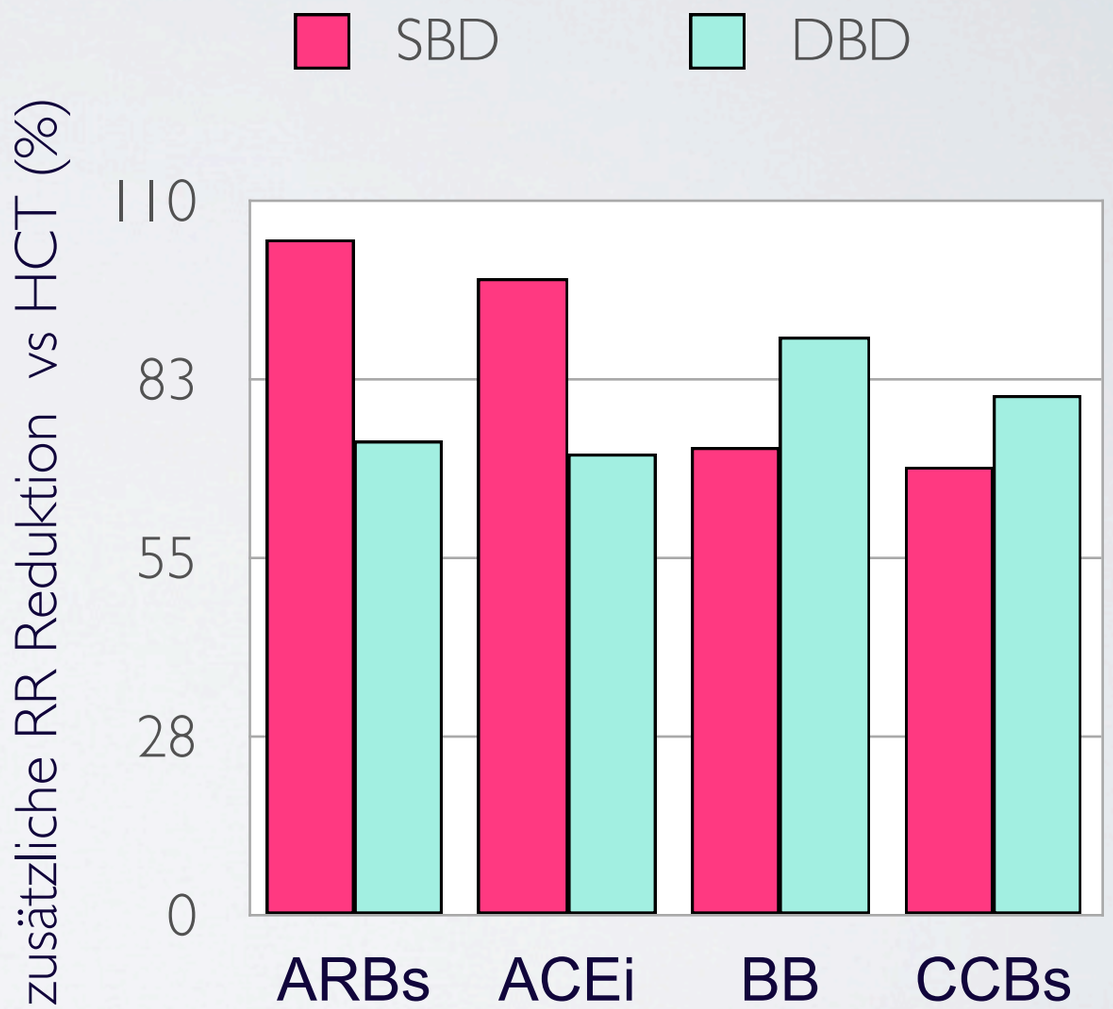
Methods: In this cross-sectional, single-center study, we enrolled 734 patients who underwent a renal angiography immediately after a coronary angiography indicated for a diagnosis of ischemic heart disease.

Results: Mean age was 64 +/- 10 years (men 72%). GFR was 79 +/- 22 ml/min per 1.73 m2. Five hundred and eighteen patients had no luminal narrowing and 216 patients had low-to-moderate luminal narrowing (10-70%, mean 36%). A positive significant association between reference diameter and GFR was detected in patients without luminal narrowing [beta 2.2 ml/min per 1.73 m2 for 1 mm increase, 95% confidence interval (CI) 0.3-4.0, P < 0.05] and in those with low-to-moderate luminal narrowing (beta 7.7 ml/min per 1.73 m2 for 1 mm increase, 95% CI 4.2-11.1, P < 0.001). The lowest quartile of reference diameter (<5.2 mm) was associated with GFR less than 60 ml/min per 1.73 m2 [odds ratio (OR) 3.18, 95% CI 1.61-6.29, P < 0.001]. Patients with resistant hypertension had low minimal diameter and reference diameter. Reference diameter less than 5.2 mm was associated with an increased risk of resistant hypertension (OR 2.63, 95% CI 1.02-6.77, P < 0.05).

Conclusions: Small renal arteries, defined by a low reference diameter or minimal luminal diameter, are independently associated with low GFR and resistant hypertension, independent of the degree of stenosis and major confounders.

IST HYDROCHLOROTHIAZID EIN SINNVOLLES ANTIHYPERTENSIVUM?

- seit 1958
- RR Senkung mies (6,5/4,5 mmHg)
- geringste Adherenz bei Diuretika
- **keine** Outcomedaten



KONTROLLRATEN

ALLHAT n = 40000

- ➡ nach 5 Jahren 34% unkontrolliert mit 2 Medik.
- ➡ am Studienende 27% ≧ 3 Medik.
- ➡ 50% mit 1-2 Medik. kontrolliert
- ➡ d.h. > 50% brauchen ≧ 3 Medik.

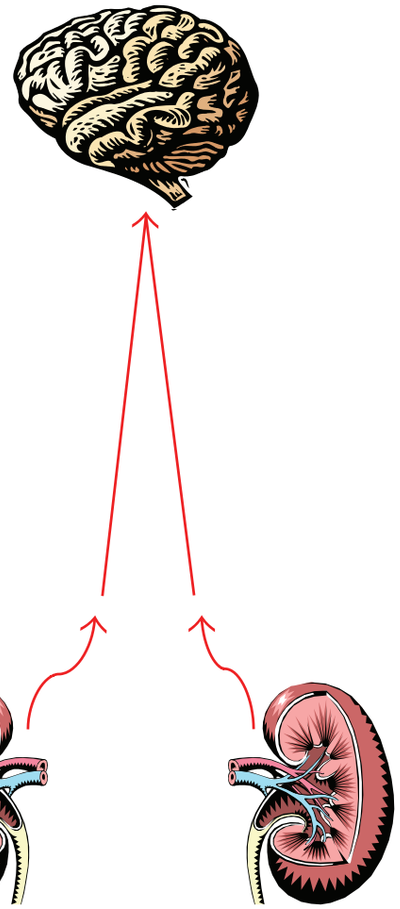
KONTROLLRATEN

Framingham n = 1959

- 32 % systolisch
- 89 % diastolisch
- 29 % beides

Renal nerves and the SNS

Afferent renal sympathetics

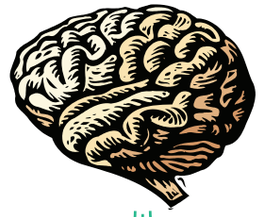


The kidney is a source of central sympathetic drive in hypertension, heart failure, chronic kidney disease, and ESRD

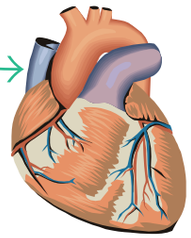
(a)

Renal nerves and the SNS

Efferent sympathetic activation

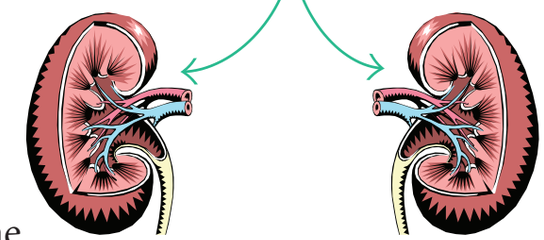


↑ Vasoconstriction



↑ HR
↑ Contractility

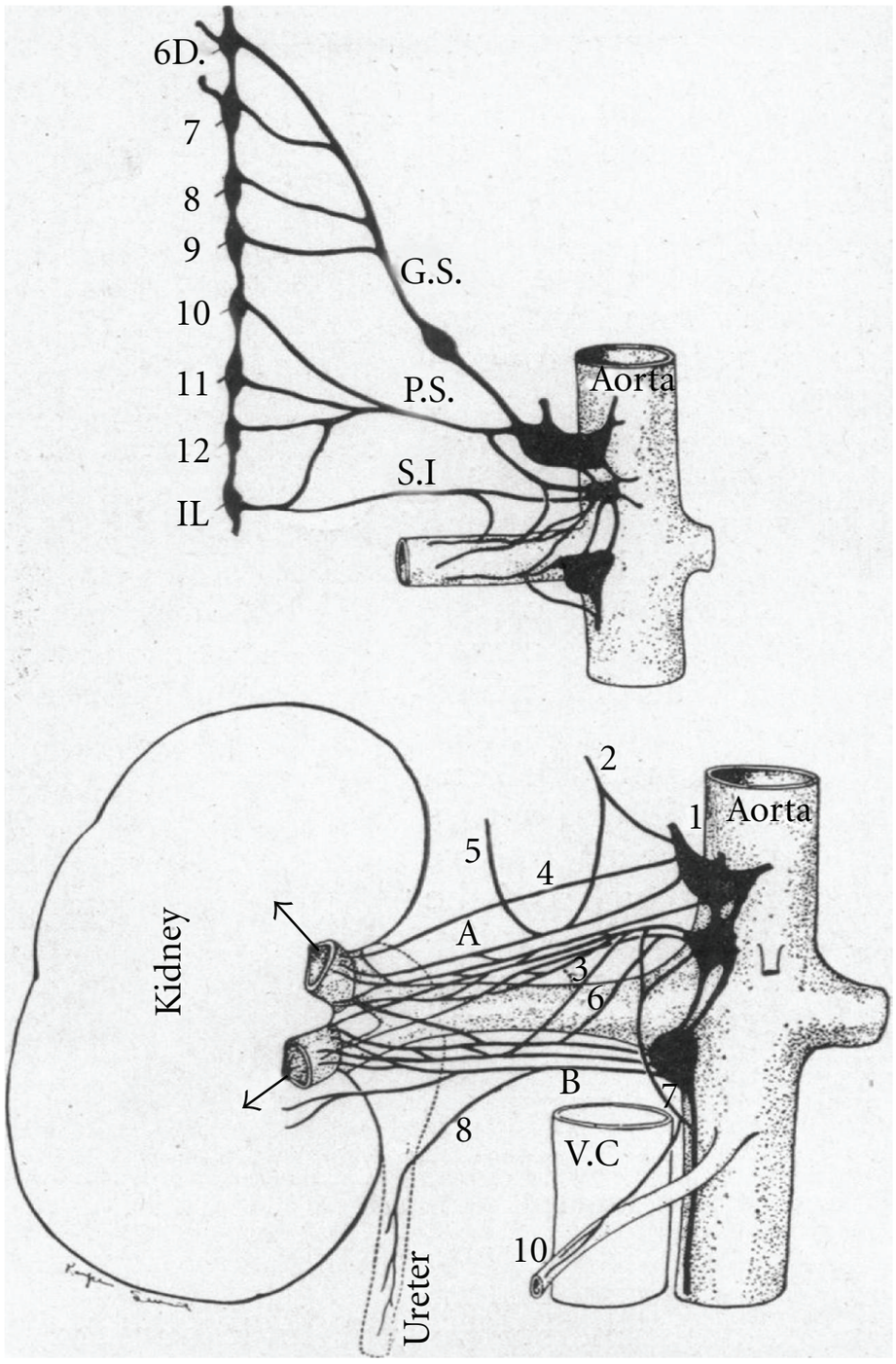
↓ RBF/GFR
↑ Renin
↑ Na^+/volume



Patients cannot develop and/or maintain elevated BP without renal involvement

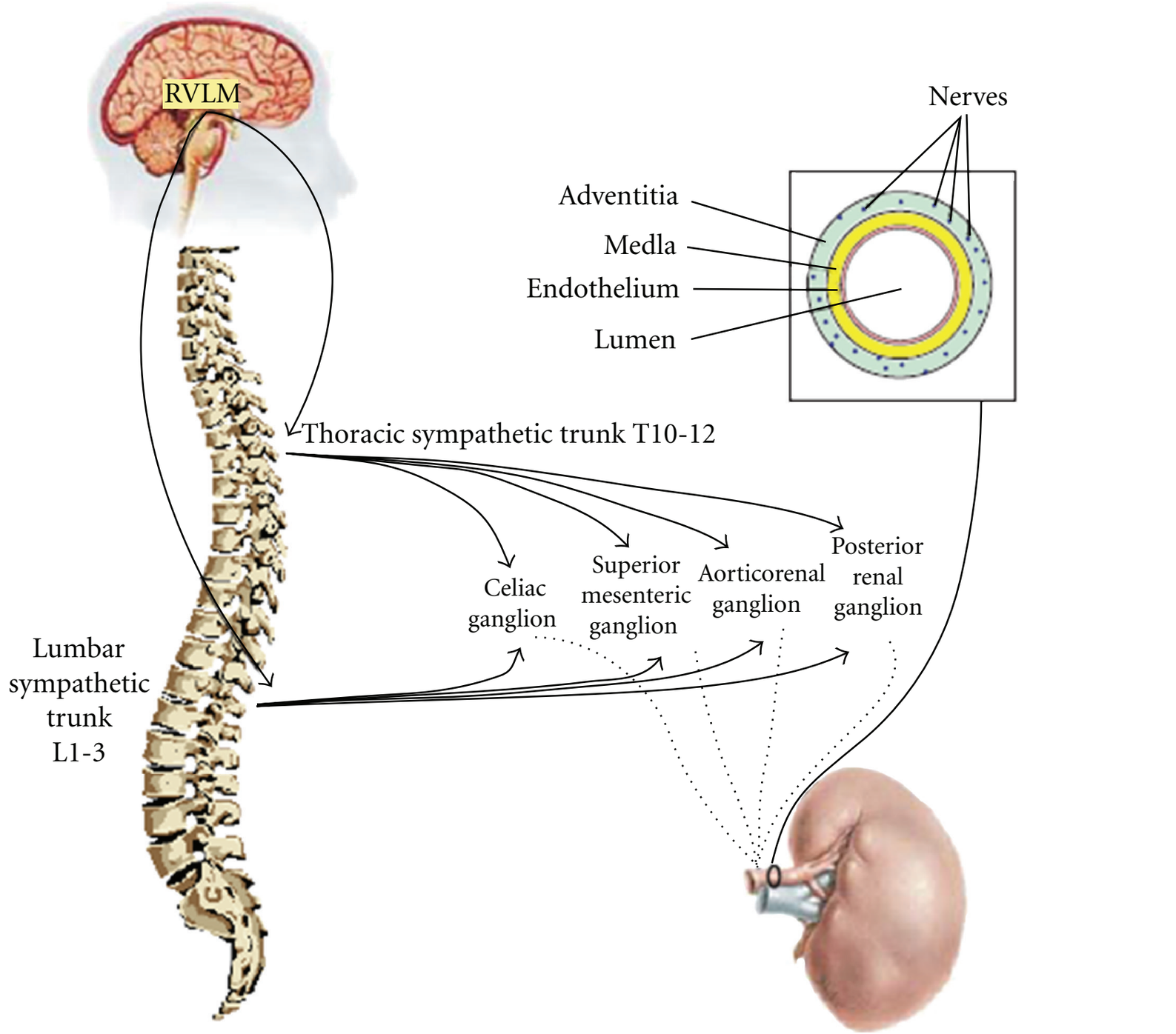
(b)

Sympathetic innervation of the kidney



Gibson, Calif Med1936

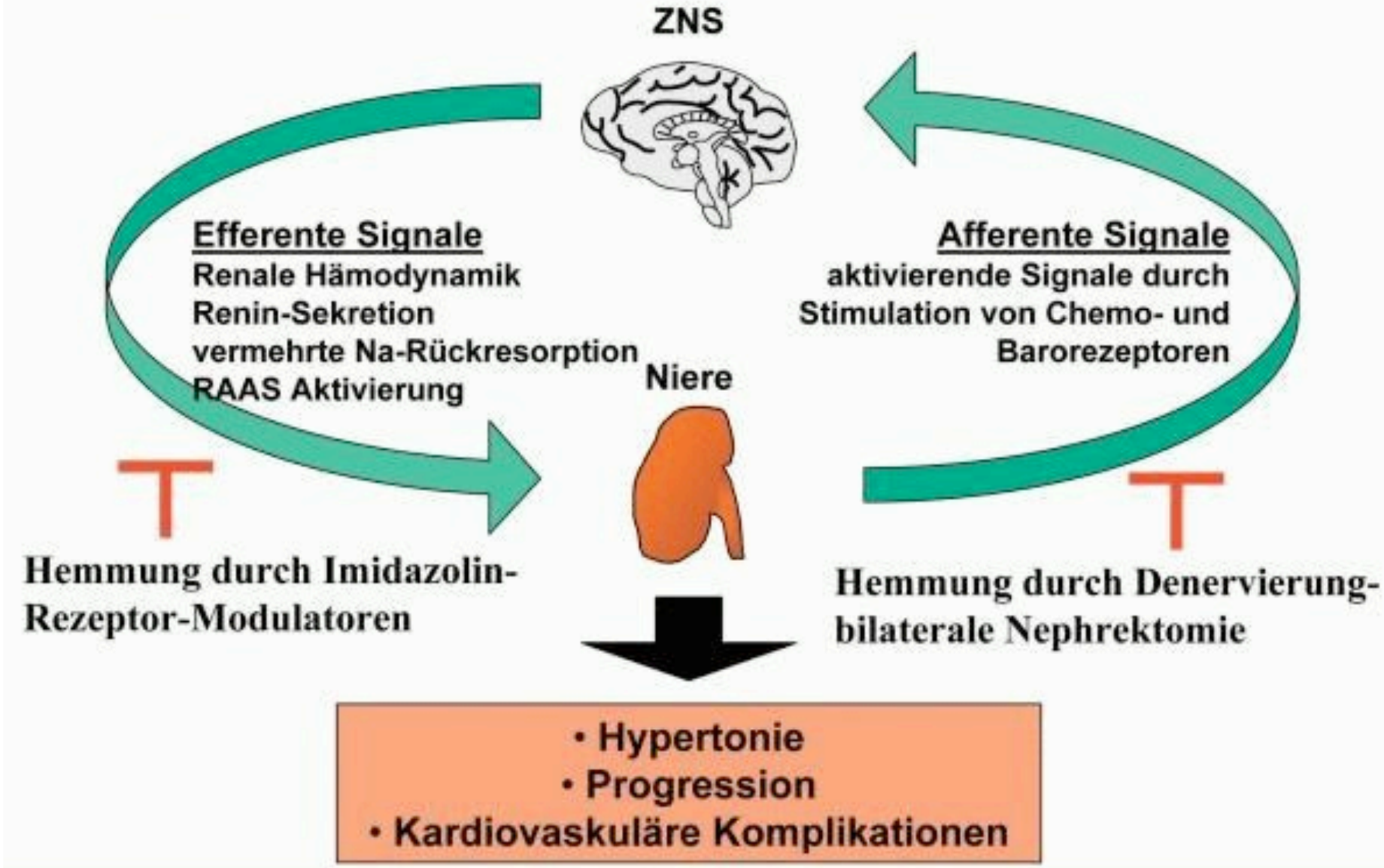
(a)



Dumas/Papademetriou, Am J Cardiol 2010 sympathetic

(b)

Sympathikus und Niere



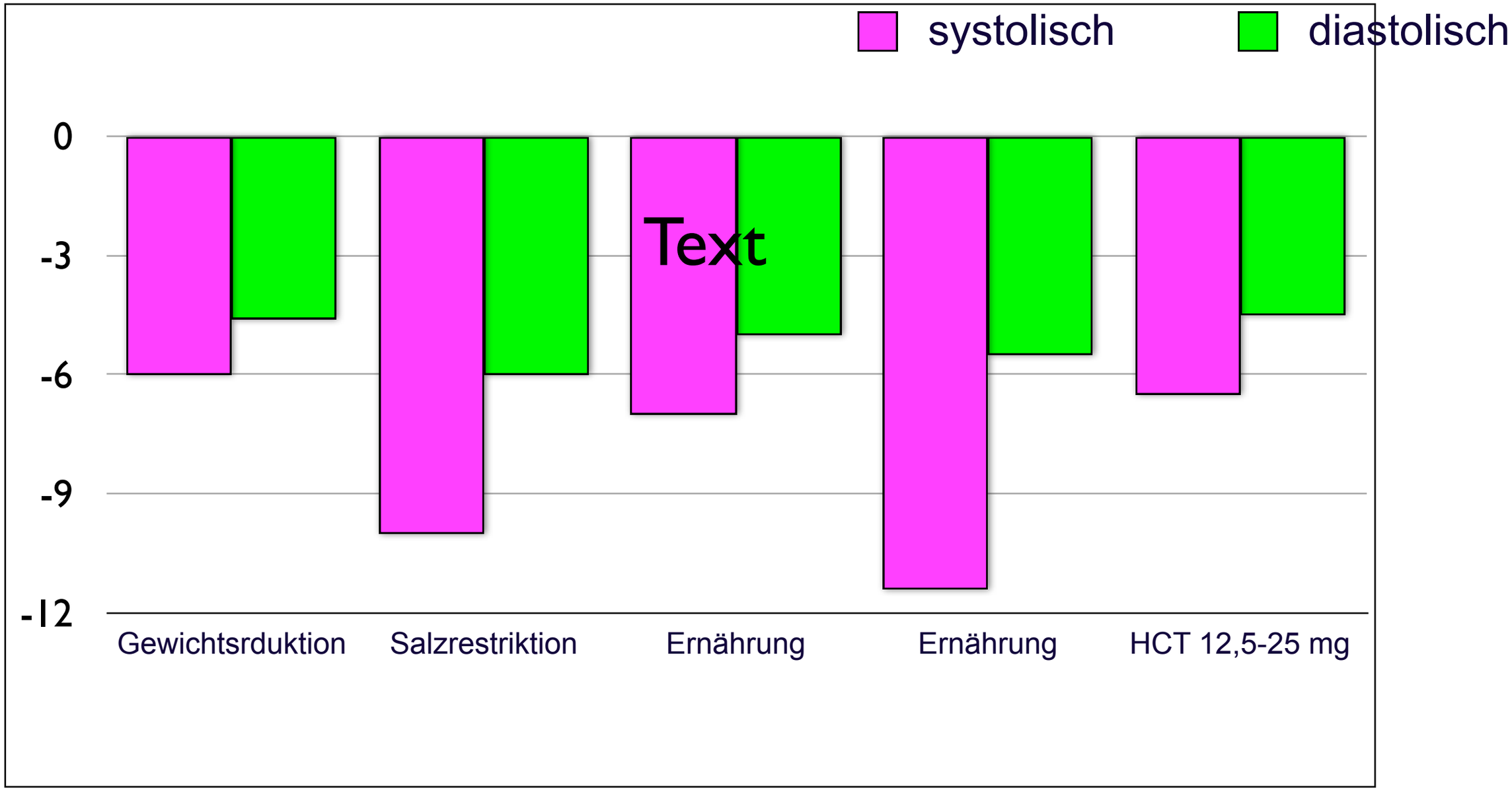
RosenkranzA Journal für Hypertonie 2004; 8 (Sonderheft 2): 17-19 ©

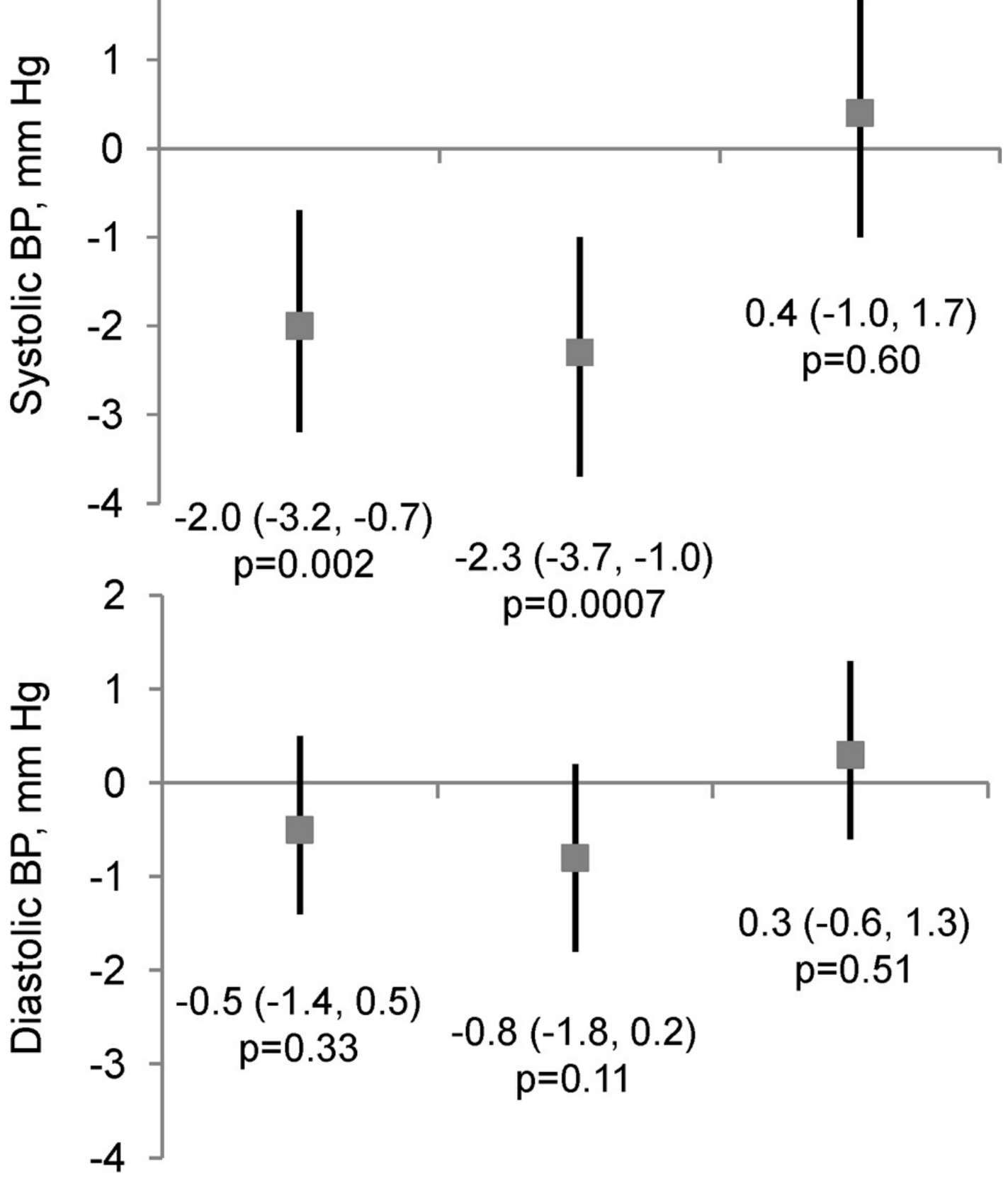
SIMPLICITY
PROOF OF CONCEPT

- 24 Zentren, 106 pt, 18-85 Jahre
- RR >160, >150 , falls Diabetes Typ2
- >3 Antihypertensiva , Diuretikum incl.
- Ex: GFR <45ml/min, abnormale Anatomie
- 1° Endpunkt: Office RR sys nach 6 Monaten

Nicht Pharmakologisch

Lifestyle




Systolic BP, mm Hg
1
0
-1
-2
-3
-4
-2.0 (-3.2, -0.7)
p=0.002
-2.3 (-3.7, -1.0)
p=0.0007
0.4 (-1.0, 1.7)
p=0.60
Diastolic BP, mm Hg
2
1
0
-1
-2
-3
-4
-0.5 (-1.4, 0.5)
p=0.33
-0.8 (-1.8, 0.2)
p=0.11
0.3 (-0.6, 1.3)
p=0.51
Soy Protein vs. Carbohydrate
Milk Protein vs. Carbohydrate
Soy Protein vs. Milk Protein

SYMPATHIKUSABLATION

Hauptergebnis

- RR nach 6 Monaten um 32/12 mmHg gesenkt
- dramatische Reduktion kardiovaskulärer Ereignisse

ERGEBNISSE

Sympathikusablation
Wirkmechanismus

Renaler Plasmafluss ↓

Reninaktivität ↓

↓

Natriumreabsorption ↓

↓

Natriurese ↑