Antihypertensiva bei spezifischen Indikationen

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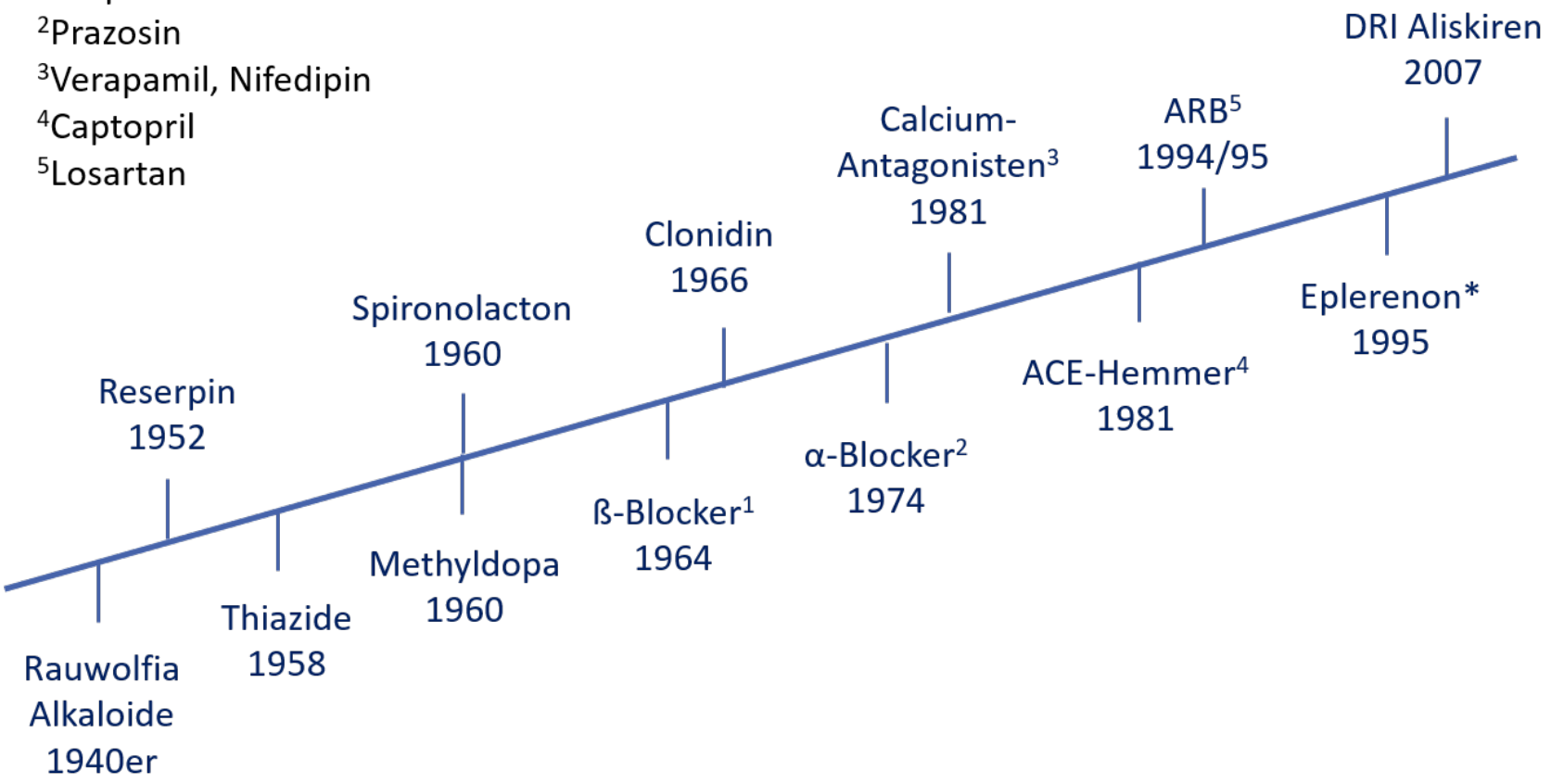
Deutschen Hochdruckliga GmbH

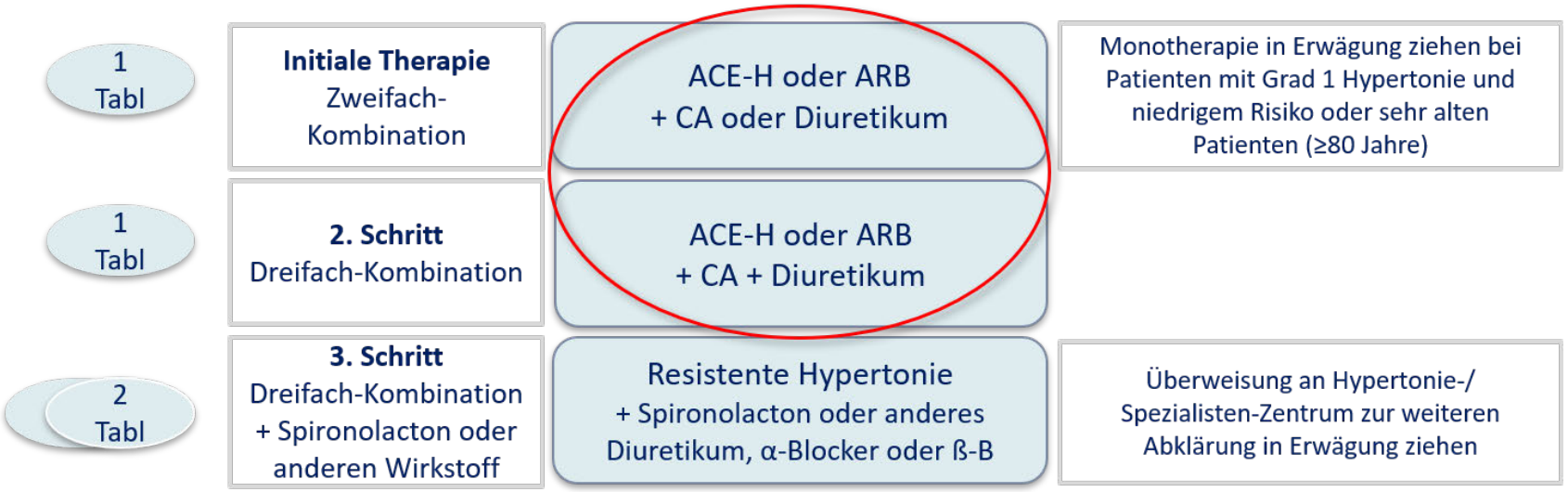
Entwicklung der antihypertensiven Therapie

[1]Propranolol
[2]Prazosin
[3]Verapamil, Nifedipin
[4]Captopril
[5]Losartan



Adaptiert nach Düsing, Kardiologe 2010; 4:27

Aktuelle Leitlinie: Behandlungsalgorithmus der medikamentösen Hypertoniebehandlung



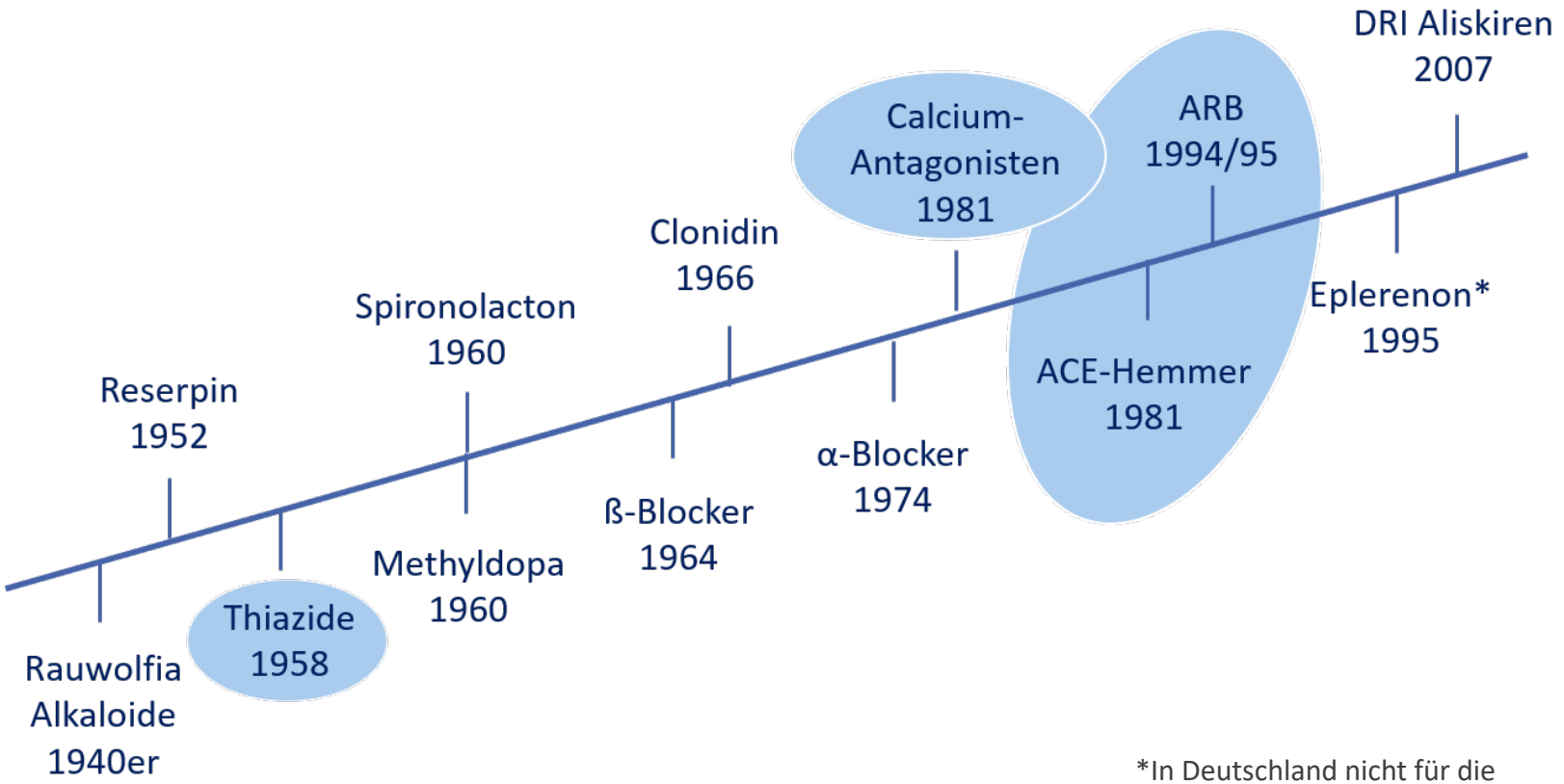
ACE-H, ACE Hemmer
ARB, Angiotensin-Rezeptorblocker
CA, Calciumantagonist
ß-B, ß-Blocker

ESH European Society of Hypertension

ESC European Society of Cardiology

ESH/ESC, J Hypertens 2018; 36:1953

Entwicklung der antihypertensiven Therapie
Primär einzusetzende Antihypertensiva

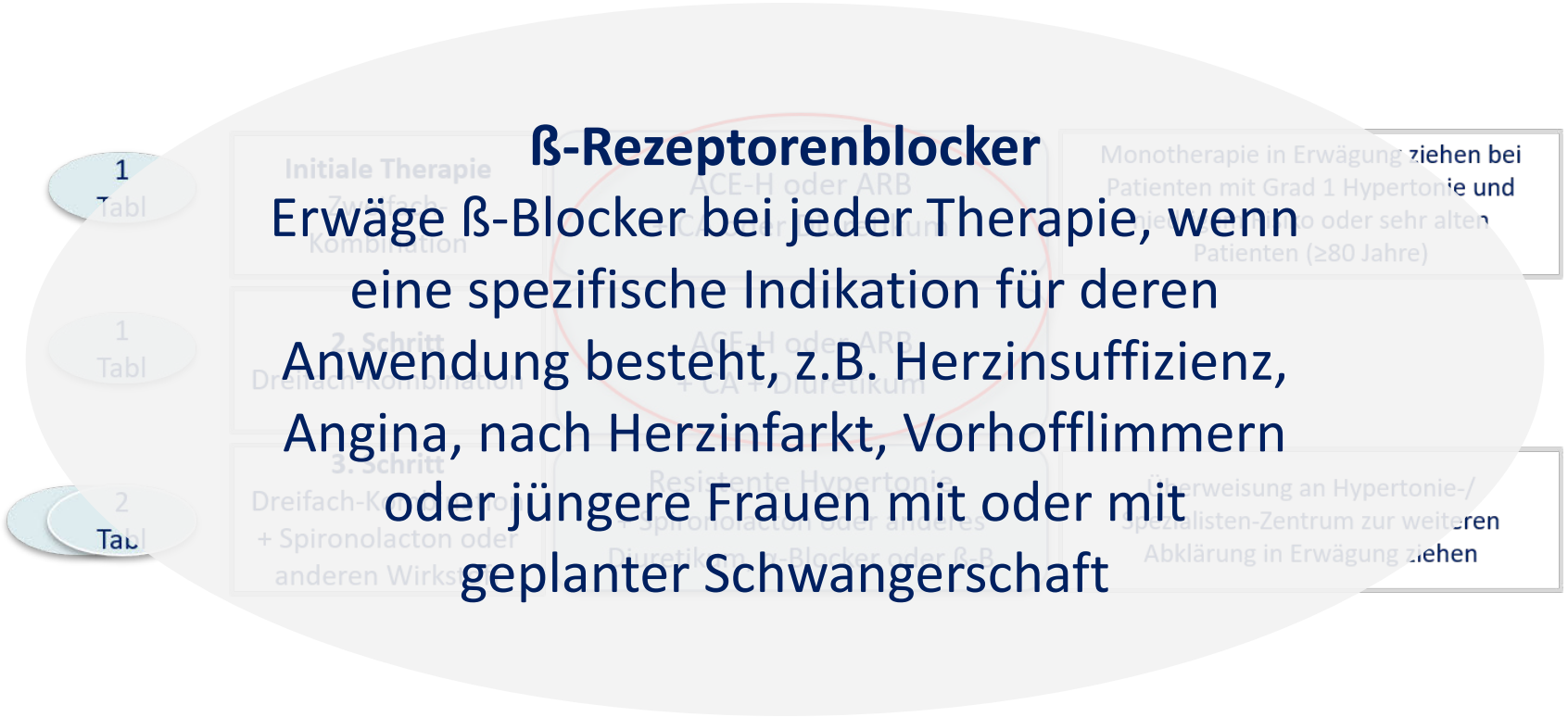


*In Deutschland nicht für die Indikation Hypertonie zugelassen
ARB, Angiotensin-Rezeptorblocker
DRI, Direkter Renin-Inhibitor

Antihypertensiva bei spezifischen Indikationen

- **ß-Rezeptorenblocker**
  - z.B. Bisoprolol, Metoprolol, Nebivolol
- **Mineralokortikoid-Rezeptorantagonisten (MRA)**
  - Spironolacton, Eplerenon
- **Schleifendiuretika**
  - z.B. Furosemid, Piretanid, Torasemid
- **Nicht-Dihydropyridin Calciumantagonisten**
  - Verapamil, Diltiazem
- **α1-Rezeptorenblocker**
  - z.B. Doxazosin, Prazosin
- **Antisympathotonika**
  - Methyldopa, Clonidin, Moxonidin

Aktuelle Leitlinie: Behandlungsalgorithmus der medikamentösen Hypertoniebehandlung



ß-Rezeptorenblocker

Erwäge ß-Blocker bei jeder Therapie, wenn eine spezifische Indikation für deren Anwendung besteht, z.B. Herzinsuffizienz, Angina, nach Herzinfarkt, Vorhofflimmern oder jüngere Frauen mit oder mit geplanter Schwangerschaft

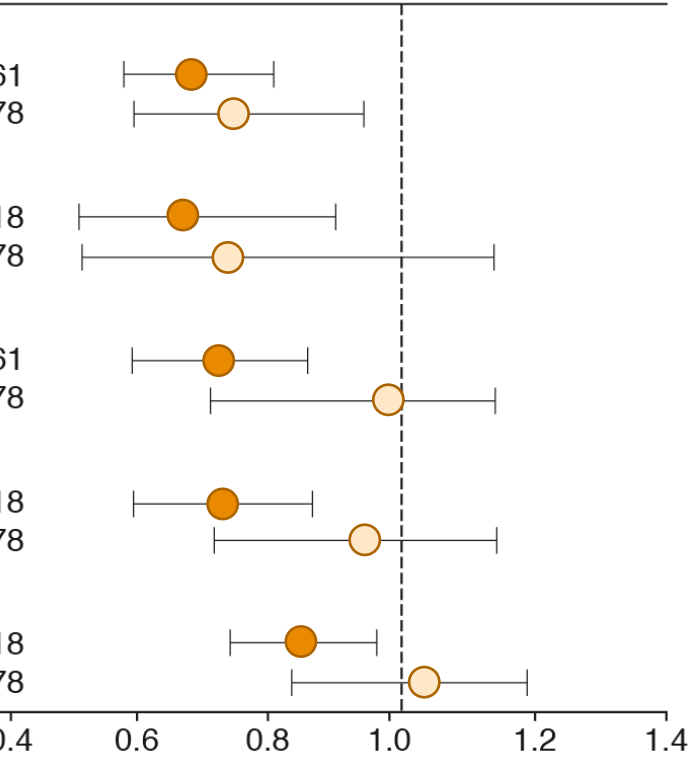
ACE-H, ACE Hemmer
ARB, Angiotensin-Rezeptorblocker
CA, Calziumantagonist
ß-B, ß-Blocker

ESH/ESC, J Hypertens 2018; 36:1953

Metaanalyse 1998
ß-Blocker bei älteren Patienten mit Hypertonie?

10 Studien mit 15.164 Patienten (≥ 65 Jahre)

Outcome First Drug	No. of Trials	Active Treatment Events/ No. of Patients	Control Events/ No. of Patients
Cerebrovascular Events			
Diuretics	8	222/5876	412/6661
β-Blockers	2	79/1521	178/2678
Stroke Mortality			
Diuretics	7	69/5838	122/6618
β-Blockers	2	25/1521	57/2678
Coronary Heart Disease			
Diuretics	8	365/5876	531/6661
β-Blockers	2	115/1521	197/2678
Cardiovascular Mortality			
Diuretics	7	332/5838	510/6618
β-Blockers	2	130/1521	230/2678
All-Cause Mortality			
Diuretics	7	681/5838	907/6618
β-Blockers	2	227/1521	384/2678



Messerli et al., JAMA 1998; 279:1903

Metaanalyse 1998
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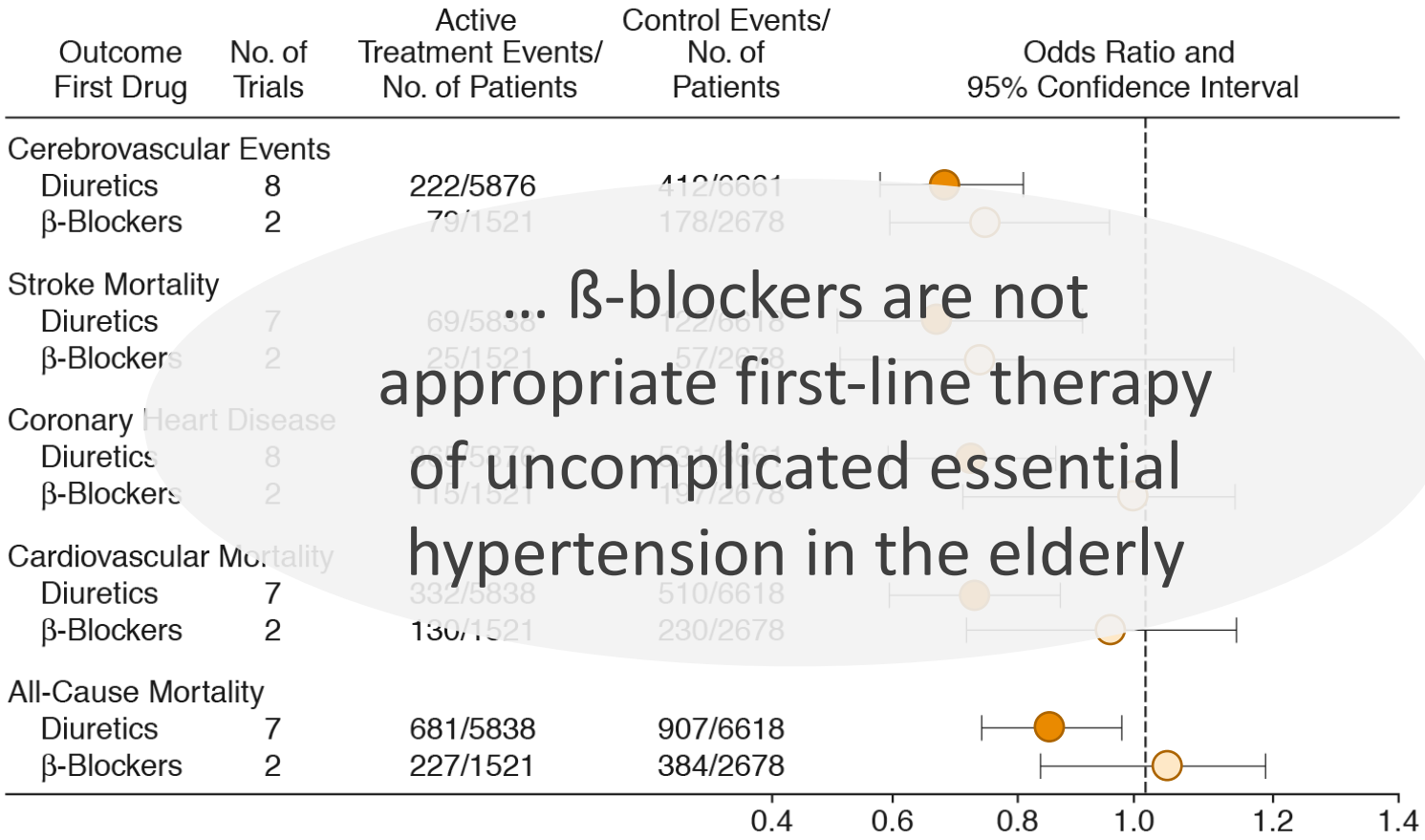

… ß-blockers are not appropriate first-line therapy of uncomplicated essential hypertension in the elderly

Messerli et al., JAMA 1998; 279:1903

Metaanalyse 2005

Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis

Lars Hjalmar Lindholm, Bo Carlberg, Ola Samuelsson

Summary

Background: β blockers have been used widely in the treatment of hypertension and are recommended as first-line drugs in hypertension guidelines. However, a preliminary analysis has shown that atenolol is not very effective in hypertension. We aim to substantially enlarge the data on atenolol and analyse the effect of different β blockers.

Methods: The Cochrane Library and PubMed were searched for β blocker treatment in patients with primary hypertension. Data were then entered into the Cochrane Collaboration Review Manager package and were summarised in meta-analyses. 13 randomised controlled trials (n=105 951) were included in a meta-analysis comparing treatment with β blockers with other antihypertensive drugs. Seven studies (n=27 433) were included in a comparison of β blockers and placebo or no treatment.

Findings: The relative risk of stroke was 16% higher for β blockers (95% CI 4–30%) than for other drugs. There was no difference for myocardial infarction. When the effect of β blockers was compared with that of placebo or no treatment, the relative risk of stroke was reduced by 19% for all β blockers (7–29%), about half that expected from previous hypertension trials. There was no difference for myocardial infarction or mortality.

Interpretation: In comparison with other antihypertensive drugs, the effect of β blockers is less than optimum, with a raised risk of stroke. Hence, we believe that β blockers should not remain first choice in the treatment of primary hypertension and should not be used as reference drugs in future randomised controlled trials of hypertension.

Lancet 2005; 366: 1545–53

Published online October 18, 2005 DOI:10.1016/S0140-6736(05)67573-3

See Comment page 1510

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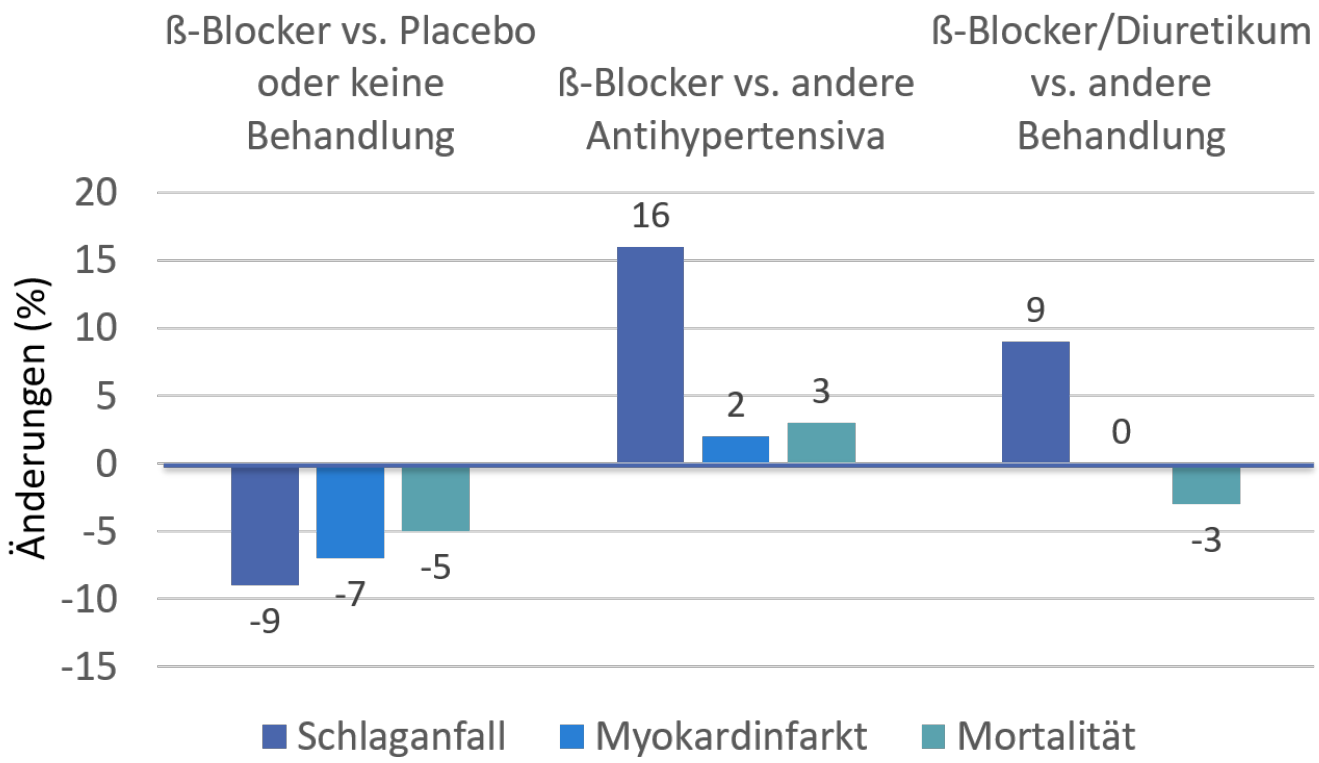
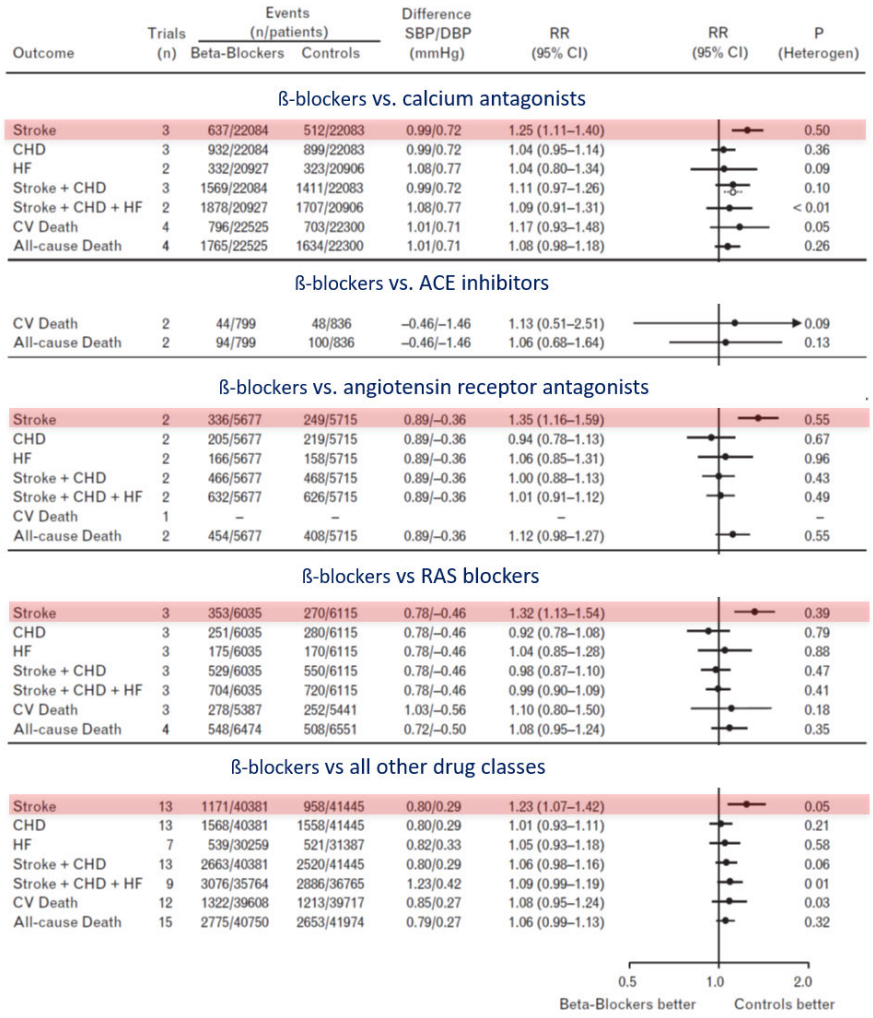
Metaanalyse 2005: ß-Blocker bei Hypertonie

13 kontrollierte Studien (n=105.951): ß-Blocker vs. andere Therapeutika
7 Studien (n=27.433) ß-Blocker vs. Placebo oder keine Behandlung



Lindholm et al., Lancet 2005; 366:1545

Metaanalyse 2015: ß-Blocker bei Hypertonie

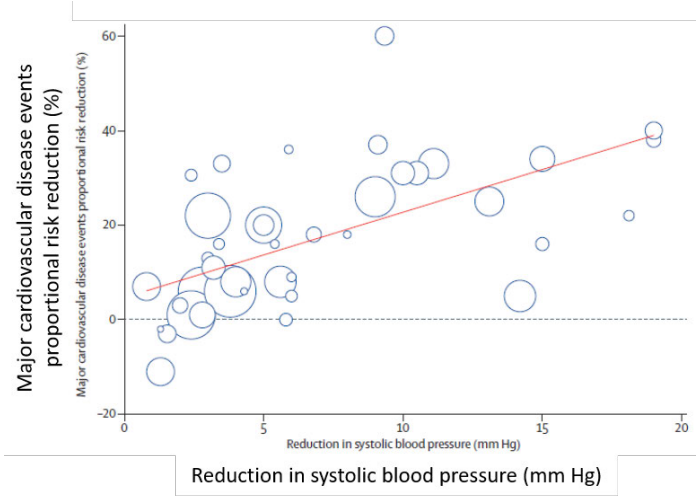


Outcome	Trials (n)	Events (n/patients) Beta-Blockers	Events (n/patients) Controls	Difference SBP/DBP (mmHg)	RR (95% CI)	P (Heterogen)
ß-blockers vs. calcium antagonists						
Stroke	3	637/22084	512/22083	0.99/0.72	1.25 (1.11–1.40)	0.50
CHD	3	932/22084	899/22083	0.99/0.72	1.04 (0.95–1.14)	0.36
HF	2	332/20927	323/20906	1.08/0.77	1.04 (0.80–1.34)	0.09
Stroke + CHD	3	1569/22084	1411/22083	0.99/0.72	1.11 (0.97–1.26)	0.10
Stroke + CHD + HF	2	1878/20927	1707/20906	1.08/0.77	1.09 (0.91–1.31)	< 0.01
CV Death	4	796/22525	703/22300	1.01/0.71	1.17 (0.93–1.48)	0.05
All-cause Death	4	1765/22525	1634/22300	1.01/0.71	1.08 (0.98–1.18)	0.26
ß-blockers vs. ACE inhibitors						
CV Death	2	44/799	48/836	–0.46/–1.46	1.13 (0.51–2.51)	0.09
All-cause Death	2	94/799	100/836	–0.46/–1.46	1.06 (0.68–1.64)	0.13
ß-blockers vs. angiotensin receptor antagonists						
Stroke	2	336/5677	249/5715	0.89/–0.36	1.35 (1.16–1.59)	0.55
CHD	2	205/5677	219/5715	0.89/–0.36	0.94 (0.78–1.13)	0.67
HF	2	166/5677	158/5715	0.89/–0.36	1.06 (0.85–1.31)	0.96
Stroke + CHD	2	466/5677	468/5715	0.89/–0.36	1.00 (0.88–1.13)	0.43
Stroke + CHD + HF	2	632/5677	626/5715	0.89/–0.36	1.01 (0.91–1.12)	0.49
CV Death	1	–	–		–	–
All-cause Death	2	454/5677	408/5715	0.89/–0.36	1.12 (0.98–1.27)	0.55
ß-blockers vs RAS blockers						
Stroke	3	353/6035	270/6115	0.78/–0.46	1.32 (1.13–1.54)	0.39
CHD	3	251/6035	280/6115	0.78/–0.46	0.92 (0.78–1.08)	0.79
HF	3	175/6035	170/6115	0.78/–0.46	1.04 (0.85–1.28)	0.88
Stroke + CHD	3	529/6035	550/6115	0.78/–0.46	0.98 (0.87–1.10)	0.47
Stroke + CHD + HF	3	704/6035	720/6115	0.78/–0.46	0.99 (0.90–1.09)	0.41
CV Death	3	278/5387	252/5441	1.03/–0.56	1.10 (0.80–1.50)	0.18
All-cause Death	4	548/6474	508/6551	0.72/–0.50	1.08 (0.95–1.24)	0.35
ß-blockers vs all other drug classes						
Stroke	13	1171/40381	958/41445	0.80/0.29	1.23 (1.07–1.42)	0.05
CHD	13	1568/40381	1558/41445	0.80/0.29	1.01 (0.93–1.11)	0.21
HF	7	539/30259	521/31387	0.82/0.33	1.05 (0.93–1.18)	0.58
Stroke + CHD	13	2663/40381	2520/41445	0.80/0.29	1.06 (0.98–1.16)	0.06
Stroke + CHD + HF	9	3076/35764	2886/36765	1.23/0.42	1.09 (0.99–1.19)	0 01
CV Death	12	1322/39608	1213/39717	0.85/0.27	1.08 (0.95–1.24)	0.03
All-cause Death	15	2775/40750	2653/41974	0.79/0.27	1.06 (0.99–1.13)	0.32

50 randomisierte, kontrollierte Studien mit 58 Vergleichen von 2 Medikamentenklassen (247.006 Patienten mit 1.029.768 Patienten-Jahren)

Thomopoulos et al., J Hypertens 2015, 33:1321

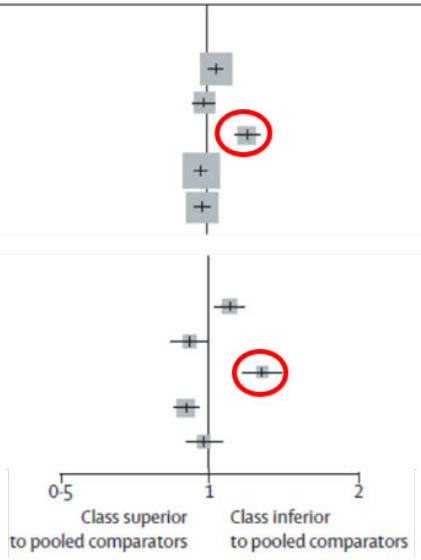
Metaanalyse 2016: Blutdrucksenkung und Prävention kardiovaskulärer Erkrankungen



Reduction in systolic blood pressure (mm Hg)

123 Studien mit 613.815 Patienten

	Studies	Intervention		Control		RR (95% CI)
		Events	Participants	Events	Participants	
Major cardiovascular events						
ACE inhibitor	10	5379	31652	9766	50805	1·03 (1·00–1·06)
ARB	8	3647	27140	3779	29331	0·98 (0·93–1·02)
β blocker	9	2863	25989	2520	27231	1·17 (1·11–1·24)
CCB	21	7857	63693	12808	82904	0·97 (0·94–0·99)
Diuretic	11	5830	38353	6782	42410	0·97 (0·94–1·00)
Stroke						
ACE inhibitor	14	1502	33355	2297	52460	1·08 (1·01–1·16)
ARB	10	1150	28703	1265	30837	0·92 (0·85–0·99)
β blocker	12	1199	40953	989	42170	1·24 (1·14–1·35)
CCB	26	2245	76768	3470	96026	0·90 (0·85–0·95)
Diuretic	12	1215	41625	1409	45707	0·97 (0·90–1·05)



Ettehad et al., Lancet 2016; 387:957

Interventionsstudien mit ß-Blocker

Alle Studien mit „klassischen“ ß-Blockern, überwiegend Atenolol

Trial	Drugs compared: Beta-blocker	Drugs compared: Control
Beta-blockers vs. calcium antagonists		
ELSA	Atenolol	Lacidipine
AASK	Metoprolol	Amlodipine
INVEST	Atenolol	Verapamil SR
ASCOT	Atenolol	Amlodipine
Beta-blockers vs. ACE-inhibitors		
UKPDS	Atenolol	Captopril
AASK	Metoprolol	Ramipril
Beta-blockers vs. angiotensin receptor blockers		
LIFE	Atenolol	Losartan
COPE	Any BB	Any ARB

Trial	Drugs compared: Diuretic	Drugs compared: Control
Diuretics vs. beta-blockers		
VA-COOP	HCTZ	Propranolol
MRC-mild	BFTZ	Propranolol
IPPPSH	Any TZ	Oxprenolol
Berglund	BFTZ	Propranolol
HAPPHY	BFTZ or HCTZ	Atenolol or Metoprolol
MRC-old	HCTZ + Amil	Atenolol
USSR	Diuretics	Propranolol
COPE	Any TZ	Any BB

Thomopoulos et al., J Hypertens 2015, 33:1321

Non-Adhärenz: Die Therapie als (Mit)Ursache

Meta-Analysis

Impact of Drug Class on Adherence to Antihypertensives

Ian M. Kronish, MD, MPH; Mark Woodward, PhD; Ziad Sergie, MD, MBA;
Gbenga Ogedegbe, MD, MPH; Louise Falzon, MLIS; Devin M. Mann, MD, MS

Background—Observational studies suggest that there are differences in adherence to antihypertensive medications in different classes. Our objective was to quantify the association between antihypertensive drug class and adherence in clinical settings.

Methods and Results—Studies were identified through a systematic search of English-language articles published from the inception of computerized databases until February 1, 2009. Studies were included if they measured adherence to antihypertensives using medication refill data and contained sufficient data to calculate a measure of relative risk of adherence and its variance. An inverse-variance–weighted random-effects model was used to pool results. Hazard ratios (HRs) and odds ratios were pooled separately, and HRs were selected as the primary outcome. Seventeen studies met inclusion criteria. The pooled mean adherence by drug class ranged from 28% for β-blockers to 65% for angiotensin II receptor blockers. There was better adherence to angiotensin II receptor blockers compared with angiotensin-converting enzyme inhibitors (HR, 1.33; 95% confidence interval, 1.13 to 1.57), calcium channel blockers (HR, 1.57; 95% confidence interval, 1.38 to 1.79), diuretics (HR, 1.95; 95% confidence interval, 1.73 to 2.20), and β-blockers (HR, 2.09; 95% confidence interval, 1.14 to 3.85). Conversely, there was lower adherence to diuretics compared with the other drug classes. The same pattern was present when studies that used odds ratios were pooled. After publication bias was accounted for, there were no longer significant differences in adherence between angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors or between diuretics and β-blockers.

Conclusion—In clinical settings, there are important differences in adherence to antihypertensives in separate classes, with lowest adherence to diuretics and β-blockers and highest adherence to angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors. However, adherence was suboptimal regardless of drug class. (***Circulation***. **2011;123:1611-1621.**)

Non-Adhärenz: Die Therapie als (Mit)Ursache

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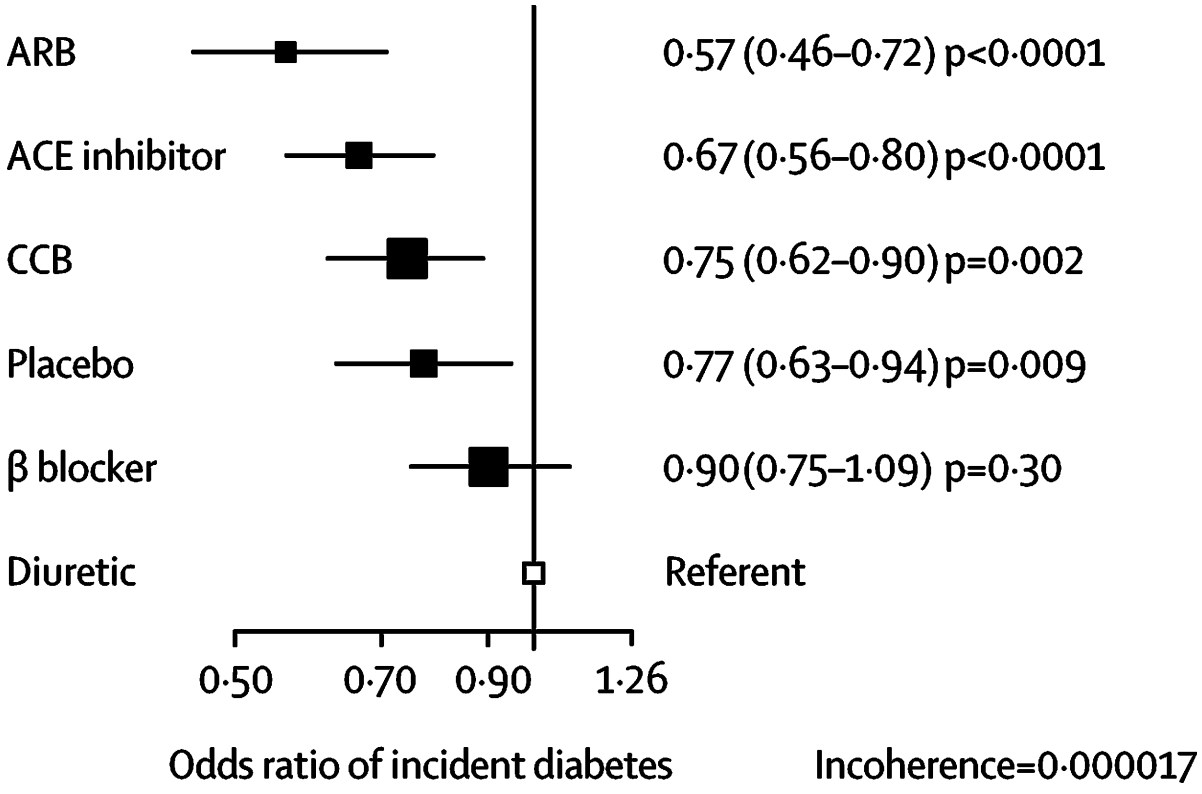
…there are important differences in adherence to antihypertensives in separate classes, with lowest adherence to diuretics and ß-blockers and highest adherence to angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors.

„New-Onset“ Diabetes in Hypertonie Interventionsstudien

Ergebnisse einer Network Metaanalyse (22 Studien, 143.153 Patienten)



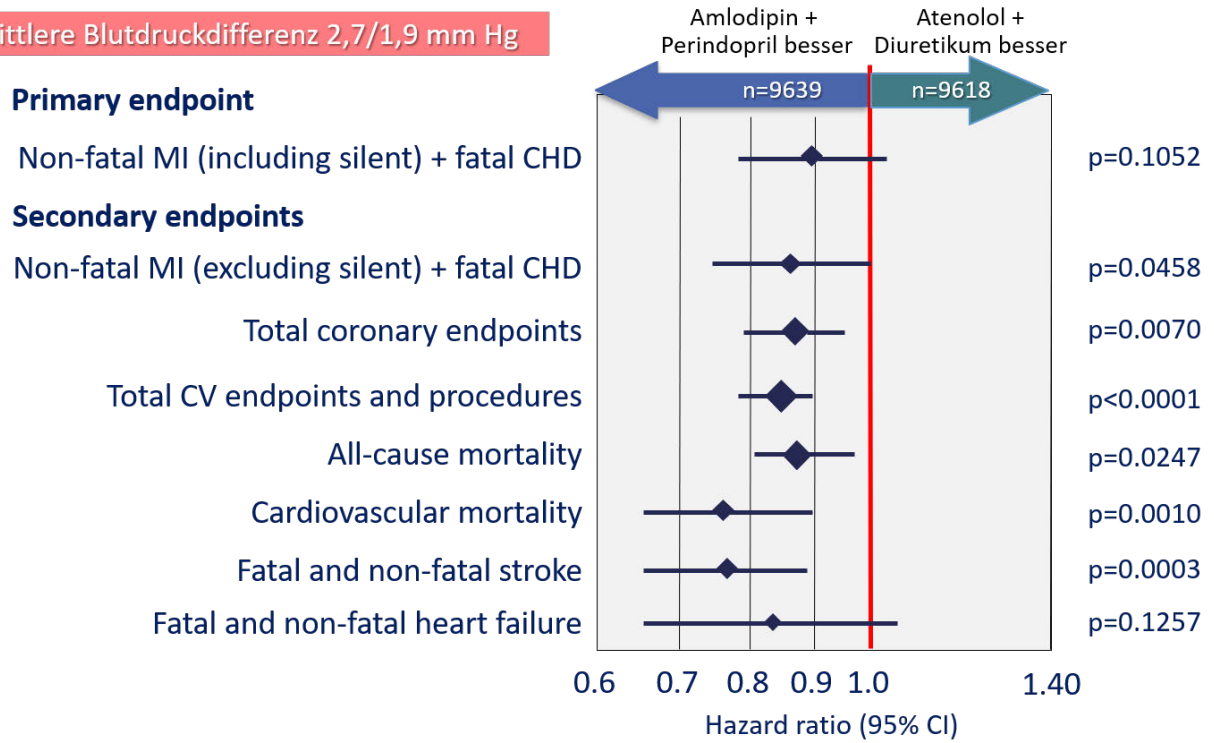
ARB, angiotensin receptor blocker
CCB, calcium channel blocker

Elliott, Meyer, Lancet 2007; 369:201

ASCOT-BPLA*

19.257 Patienten, Therapiebeginn mit Amlodipin oder Atenolol, erweitert durch Zugabe von Perindopril oder Bendroflumethiazid. Zusätzlich Doxazosin bei Bedarf in beiden Gruppen. 5.5 Jahre (Median) Observation

Mittlere Blutdruckdifferenz 2,7/1,9 mm Hg

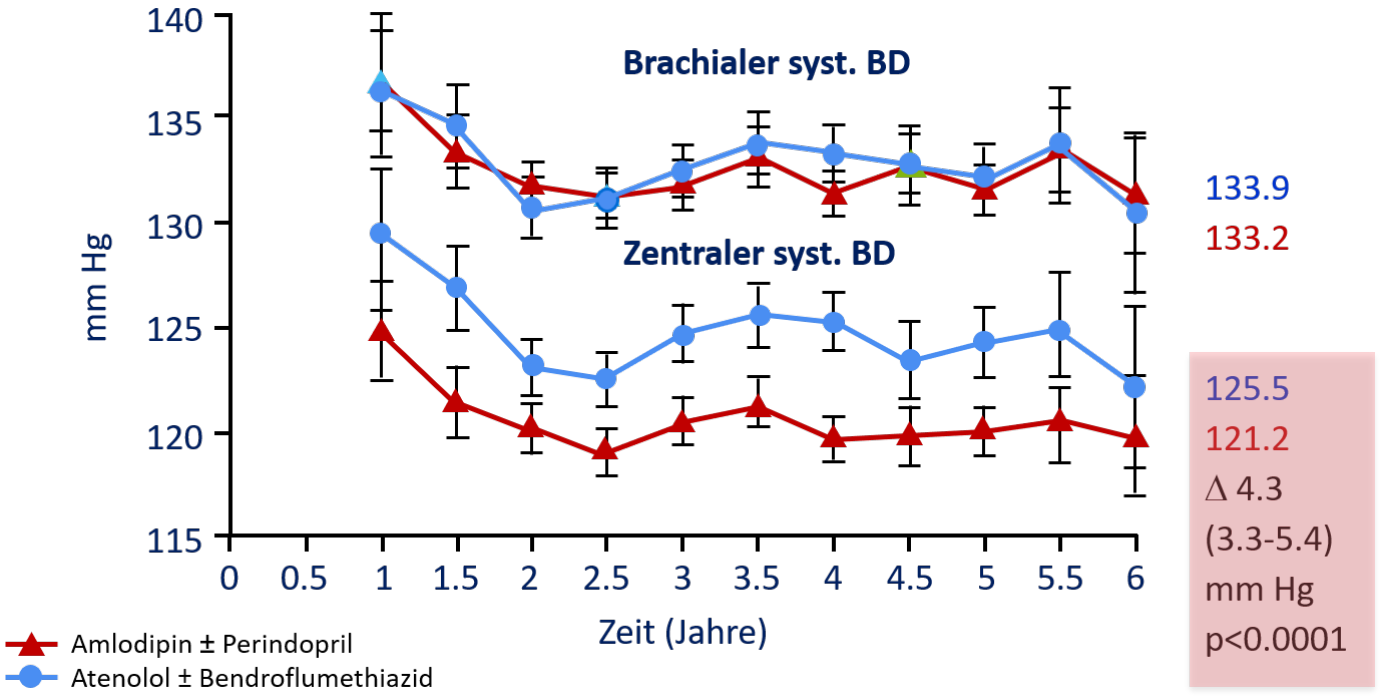


ASCOT-BPLA = Anglo-Scandinavian Cardiac Outcomes Trial - Blood Pressure Lowering Arm

Dahlöf et al., Lancet 2005; 366:895

Antihypertensiva: Unterschiedliche Effekte auf brachialen und zentralen Blutdruck

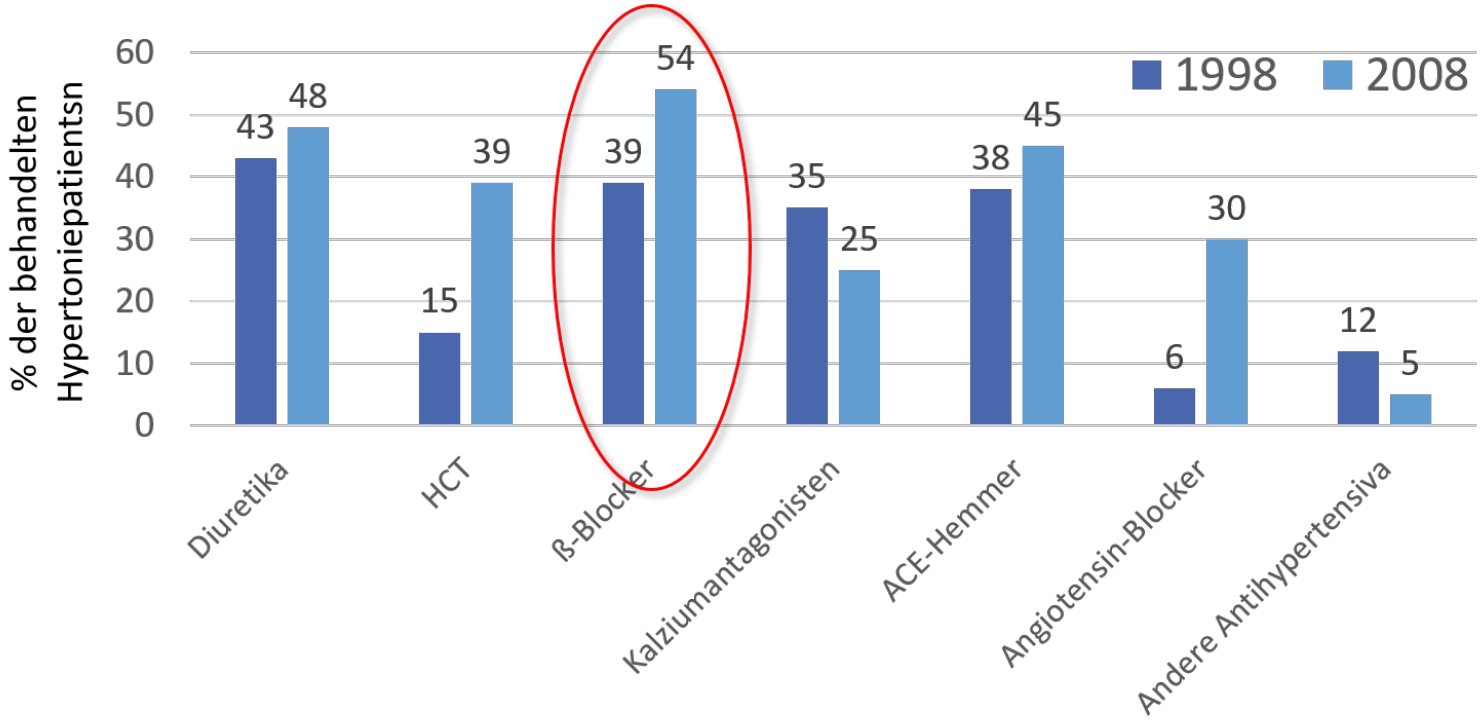
2199 Patienten von 5 ASCOT* Zentren wurden in die „Conduit Artery Function Evaluation (CAFE) Study“ eingeschlossen



*Anglo-Scandinavian Cardiac Outcomes Trial

Antihypertensiva Verordnungen in Deutschland (Mono- und Kombinationstherapie)

National Health Examination Surveys 1998 (GNHIES98) und 2008–2011 (DEGS1); Erwachsene 18–79 Jahre



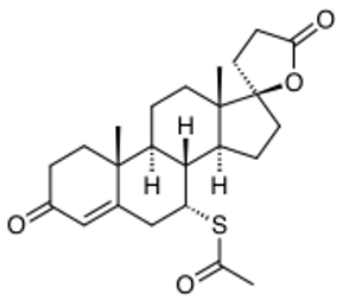
Sarganas et al., Am J Hypertens 2016; 29: 104

ß-Blocker: Keine homogene Wirkstoffklasse

- Alle ß-Blocker Interventionsstudien bei Hypertonie mit “harten” Endpunkten (z.B. Schlaganfall, Myokardinfarkt Mortalität) wurden mit klassischen ß-Blockern, überwiegend mit Atenolol, durchgeführt
- Unterschiedliche Eigenschaften von “vasodilatierenden” ß-Blockern (z.B. Carvedilol und Nebivolol)
- Nebivolol: Günstigere Effekte auf den zentralen Blutdruck, keine gesteigerte Rate an „new onset“ Diabetes und besseres Nebenwirkungsprofil als klassische ß-Blocker
- Sowohl Carvedilol und Nebivolol bewirken bei Patienten mit Herzinsuffizienz eine Prognose-Verbesserung
- Jedoch: Keine „harten“ Endpunktstudien für diese Substanzen bei der Indikation Hypertonie

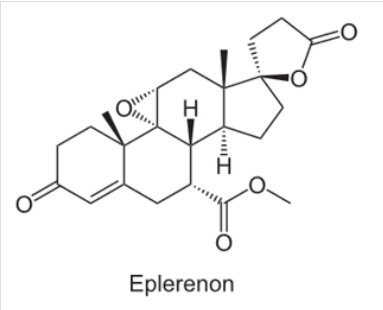
ESH/ESC, J Hypertens 2018; 36:1953

Mineralokortikoid Rezeptor Antagonisten



Spironolacton

- Zulassung: Primärer Aldosteronismus, Ödeme, Aszites
- Hemmung des Mineralokortikoidrezeptors (im distalen Tubulus)
- Cave: Hyperkaliämie insbesondere bei eingeschränkter Nierenfunktion
- Anti-androgene und progestagene Eigenschaften
- Prämenopausale Frauen: Periodenstörungen, Hirsutismus; Männer: Gynäkomastie, sexuelle Funktionsstörungen (Libido und Potenz)
- Gute Verträglichkeit bei postmenopausalen Frauen

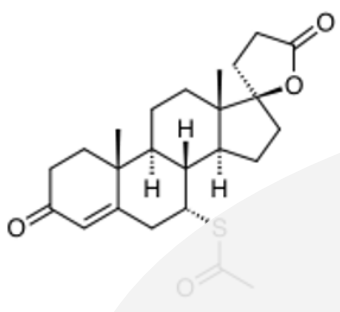


Eplerenon

- Zulassung: HFrEF (LVEF ≤40 %) nach kürzl. aufgetr. Herzinfarkt (EPHESUS-Studie[1]), HFrEF im Stadium NYHA II und LVEF ≤30 % (EMPHASIS-HF Studie[2])
- Keine Zulassung für Hypertonie
- Hemmung des Mineralokortikoidrezeptors (im distalen Tubulus)
- Cave: Hyperkaliämie insbesondere bei eingeschränkter Nierenfunktion
- Selten: Endokrine Nebenwirkungen (Gynäkomastie, erektile Dysfunktion, Menstruationsstörungen)

Eplerenone post-acute myocardial infarction heart failure efficacy and survival study: N. Engl. J. Med. 2003; 348:1309
Eplerenone in mild patients hospitalization and survival study in heart failure. N Engl J Med 2011; 364:11

Mineralokortikoid Rezeptor Antagonisten

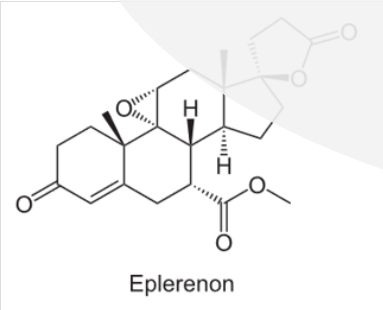


Spironolacton

- Zulassung: Primärer Aldosteronismus, Ödeme, Aszites
- Hemmung des Mineralokortikoidrezeptors (im distalen Tubulus)
- Cave: Hyperkaliämie insbesondere bei eingeschränkter Nierenfunktion
- Anti-androgene und progestagene Eigenschaften
- Prämenopausale Frauen: Menstruationsstörungen, Hirsutismus; Männer: Gynäkomastie, erektile Dysfunktion, Libido und Potenz)
- Gute Verträglichkeit bei postmenopausalen Frauen

Dosisäquivalenz:
Eplerenon : Spironolacton → 4.5 : 1
Also:
100 mg Eplerenon ~ 25 mg Spironolacton

Roush et al., J Hypertens 2016; 34: 11-16



Eplerenon

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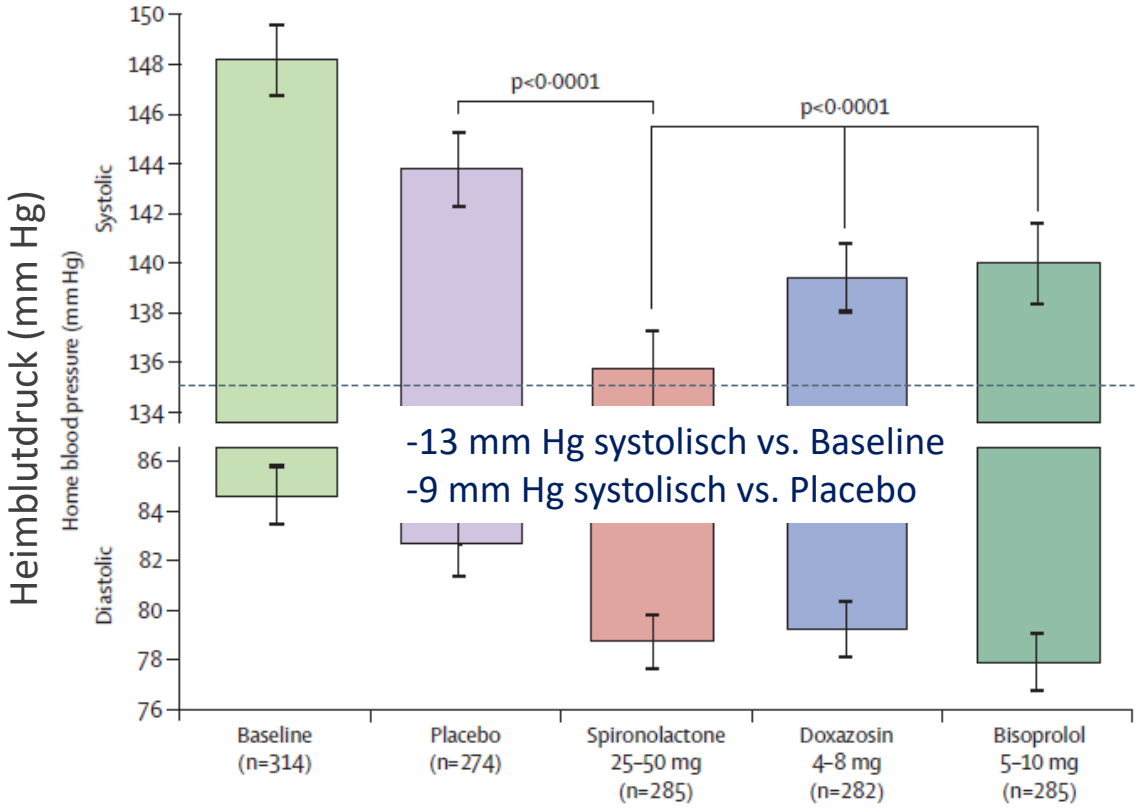
Eplerenone in mild patients hospitalization and survival study in heart failure. N Engl J Med 2011; 364:11

PATHWAY-2 Studie: Spironolacton effektivste Option bei Therapieresistenz

Medikament	**n**
Spironolacton	285
Doxazosin	282
Bisoprolol	285
Placebo	274

Je 12 Wochen Behandlung;
nach 6 Wochen Verdopplung der Dosis

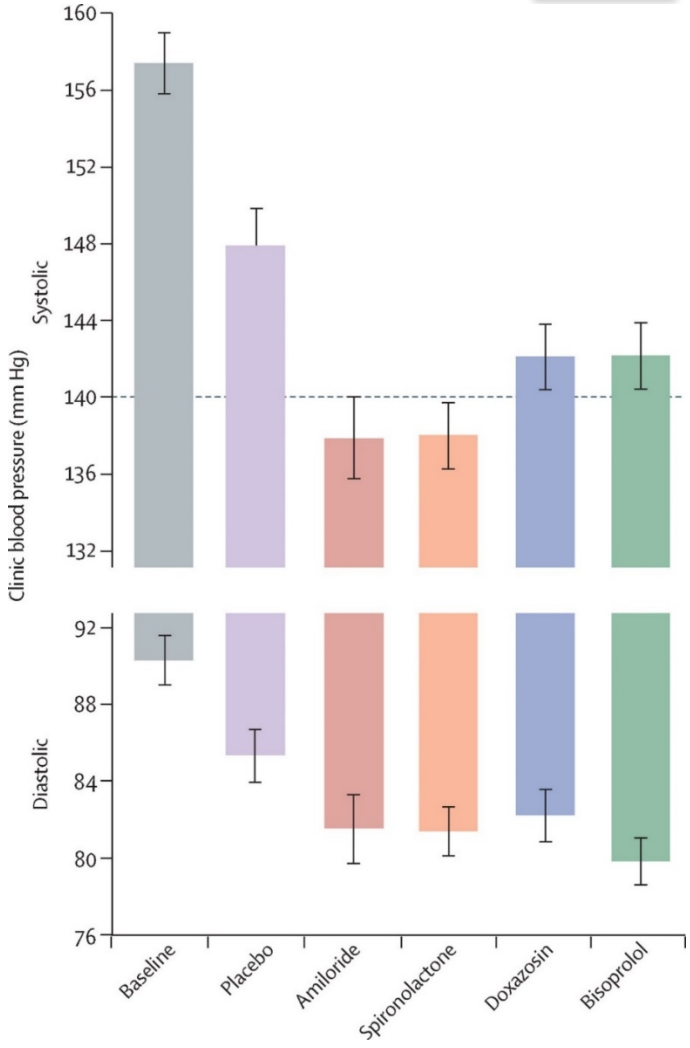
230 Patients beendeten alle 4 Therapiezyklen



Williams et al., BMJ Open, Published Online September 21, 2015

Vergleich von Placebo, Amilorid, Spironolacton, Doxazosin und Bisoprolol auf den Klinik/Praxis Blutdruck

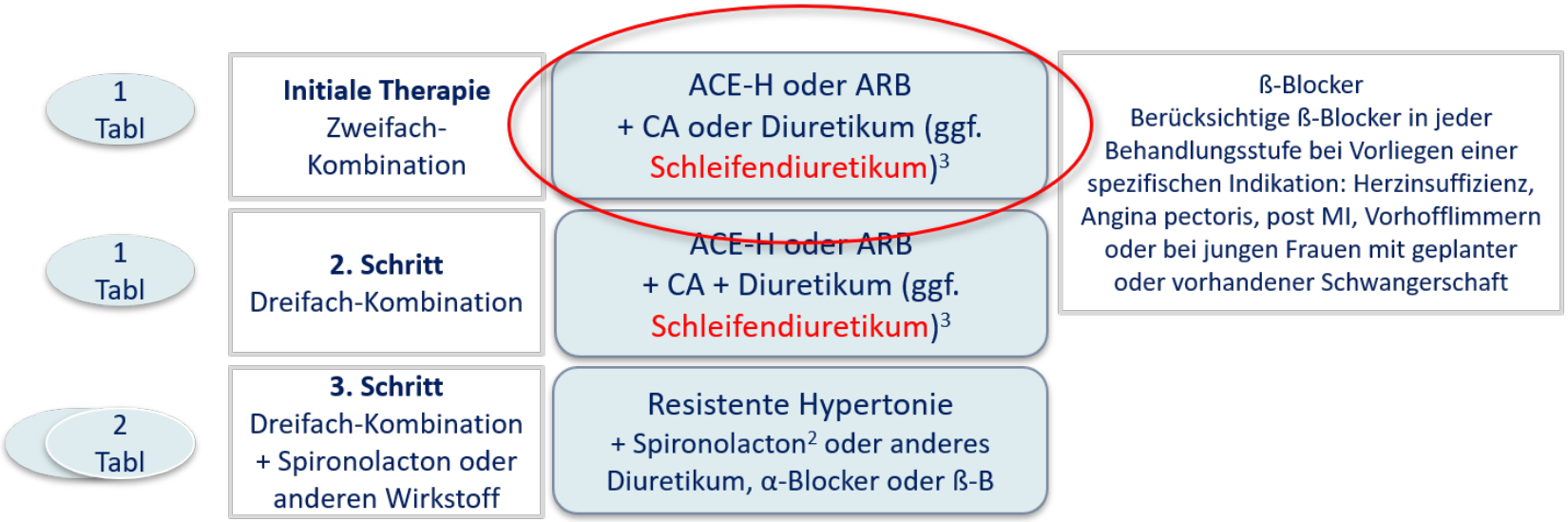
6 Wochen Behandlung
(open label runout phase)



Spironolacton und Amilorid reduzieren den systolischen und diastolischen Blutdruck vs. Placebo und vs. Doxazosin und Bisoprolol ($p < 0.0001$)

Williams et al., The Lancet Diabetes & Endocrinology DOI: (10.1016/S2213-8587(18)30071-8)

Behandlungsalgorithmus der Hypertoniebehandlung **bei CKD[1]**

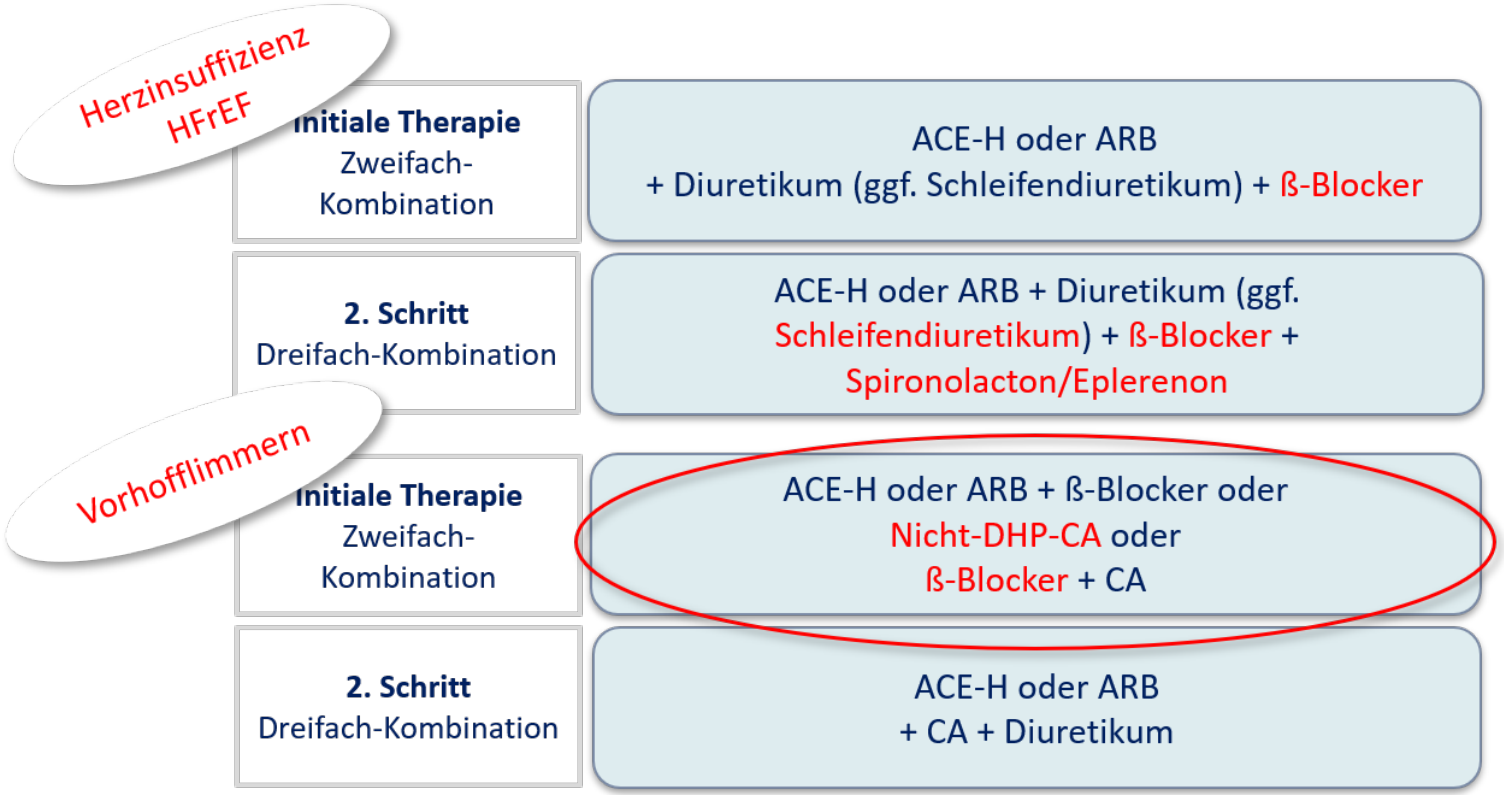


ACE-H, ACE Hemmer
ARB, Angiotensin-Rezeptorblocker
CA, Calziumantagonist
ß-B, ß-Blocker

[1] Chronische Nierenerkrankung, eGFR < 60 ml/min mit oder ohne Proteinurie
[2] Cave Hyperkaliämie bei eGFR < 45 ml/min oder Ausgangswert > 4,5 mmol/l
[3] Insbesondere bei eGFR < 30 ml/min

ESH/ESC, J Hypertens 2018; 36:1953

Behandlungsalgorithmus der Hypertoniebehandlung bei …



ACE-H, ACE Hemmer
ARB, Angiotensin-Rezeptorblocker
CA, Calciumantagonist
DHP-CA, Dihydropyridin-Calciumantagonist
ß-B, ß-Blocker

ESH European Society of Hypertension

ESC European Society of Cardiology

ESH/ESC, J Hypertens 2018; 36:1953

Diuretika: Wirkdauer, Blutdruckwirksamkeit und Effekte auf Serum Kalium

Diuretic	DOA (hours)	Dosage forms	Dose	Comparator	SBP change	Serum K change
HCTZ	8 < 24	12.5, 25, 50	25	Placebo	−9.5	0.3
CTDN	48–72	25	6.25–25	HCTZ 12.5–50	−3.0 to −10.1	−0.1
INDAP	24–34	1.25, 2.5, 5.0	1.25–5	HCTZ 12.5–50	−5.1	−0.1
TRIAM/HCTZ	<24/8 < 24	37.5/25, 50/25, 75/50	(TRIA below)	(TRIA below)	(TRIA below)	(TRIA below)
AMIL/HCTZ	24+/8 < 24	5/50	(AMIL below)	(AMIL below)	(AMIL below)	(AMIL below)
SPIR/HCTZ	24–34/8 < 24	25/25	(SPIR below)	(SPIR below)	(SPIR below)	(SPIR below)
TRIAM	<24	50, 100	50, 100	Placebo	−1.9	0.26
AMIL	24+	5	2.5–40	Placebo	−5.0 to −15.2	0.37
SPIR	24–34	25, 50, 100	25–400	Placebo	−7.6 to −24.8	0.43
EPLER	24+	25, 50	25–400	Placebo	−5.7 to −16.9	NA
Furosemide	4–6	20, 40, 80	10–80	Placebo	Less than thiazides	NA
Torsemide	12	5, 10, 20, 100	10–100	Placebo and INDAP	Comparable to thiazides	None

AMIL, amiloride; CTDN, chlorthalidone; DOA (hours), duration of action in hours; EPLER, eplerenone; HCTZ, hydrochlorothiazide; INDAP, indapamide; SBP, systolic blood pressure; SPIR, spironolactone; TRIAM, triamterene.

Roush & Sica, Am J Hypertens 2016; 29: 1130

Blood pressure-lowering efficacy of loop diuretics for primary hypertension (Review)

Cochrane Library

Cochrane Database of Systematic Reviews

Blood pressure-lowering efficacy of loop diuretics for primary hypertension (Review)

Musini VM, Rezapour P, Wright JM, Bassett K, Jauca CD

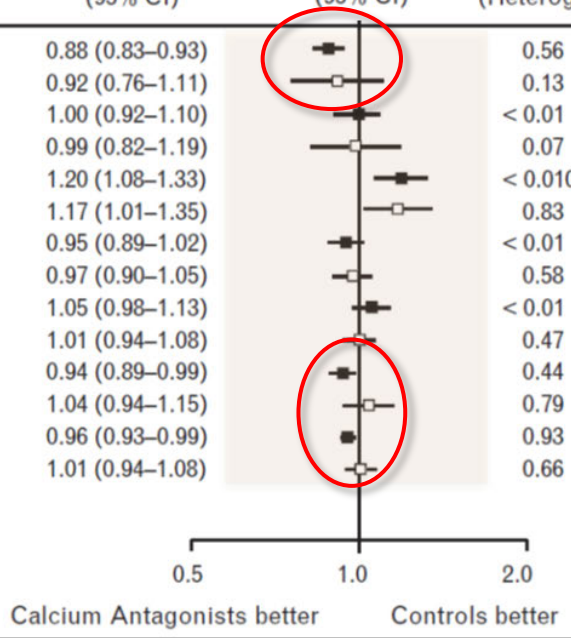
- … the SBP/DBP lowering effect of loop diuretics is -8/-4 mm Hg, likely an overestimate due to the high risk of bias in the studies and the high likelihood of publication bias
- There are no clinically meaningful blood pressure-lowering differences between different drugs within the loop diuretic class
- … no conclusions regarding the dose-related decrease in systolic and diastolic blood pressure of loop diuretics in the treatment of primary hypertension
- This review did not provide a good estimate of the incidence of harms associated with loop diuretics

Musini VM et al., 2015, Issue 5. Art. No.: CD003825. DOI: 10.1002/14651858.CD003825.pub4.

Wirksamkeit von Calciumantagonisten vs. alle anderen in Studien eingesetzten Antihypertensiva

Separate Analyse für Dihydropyridin-CA (vorwiegend Amlodipin) und Nicht-Dihydropyridin-CA (Verapamil und Diltiazem)

Outcome		Trials (n)	Events (n/patients) Calcium Antagonists	Events (n/patients) Controls	Difference SBP/DBP (mmHg)	RR (95% CI)	P (Heterogen)
Stroke	DHP	23	1661/ 49144	2844/ 66690	–0.73/–0.94	0.88 (0.83–0.93)	0.56
	N–DHP	4	469/ 25080	519/ 25309	0.82/–0.16	0.92 (0.76–1.11)	0.13
CHD	DHP	23	2187/ 49144	3773/ 66690	–0.73/–0.94	1.00 (0.92–1.10)	< 0.01
	N–DHP	4	771/ 25080	771/ 25309	0.82/–0.16	0.99 (0.82–1.19)	0.07
HF	DHP	19	1769/ 45105	2582/ 62669	–0.78/–0.99	1.20 (1.08–1.33)	< 0.010
	N–DHP	4	380/ 25080	328/ 25309	0.82/–0.16	1.17 (1.01–1.35)	0.83
Stroke + CHD	DHP	23	3845/ 49144	6617/ 66690	–0.73/–0.94	0.95 (0.89–1.02)	< 0.01
	N–DHP	5	1254/ 25383	1303/ 25610	0.83/–0.15	0.97 (0.90–1.05)	0.58
Stroke + CHD + HF	DHP	19	5452/ 45105	8998/ 62669	–0.78/–0.99	1.05 (0.98–1.13)	< 0.01
	N–DHP	4	1620/ 25080	1618/ 25309	0.82/–0.16	1.01 (0.94–1.08)	0.47
CV Death	DHP	19	1617/ 44383	3010/ 62589	–0.69/–0.96	0.94 (0.89–0.99)	0.44
	N–DHP	5	717/ 25383	694/ 25610	0.82/–0.16	1.04 (0.94–1.15)	0.79
All-cause Death	DHP	24	4088/ 49133	6908/ 67359	–0.74/–0.93	0.96 (0.93–0.99)	0.93
	N–DHP	4	1443/ 25080	1444/ 25309	0.82/–0.16	1.01 (0.94–1.08)	0.66



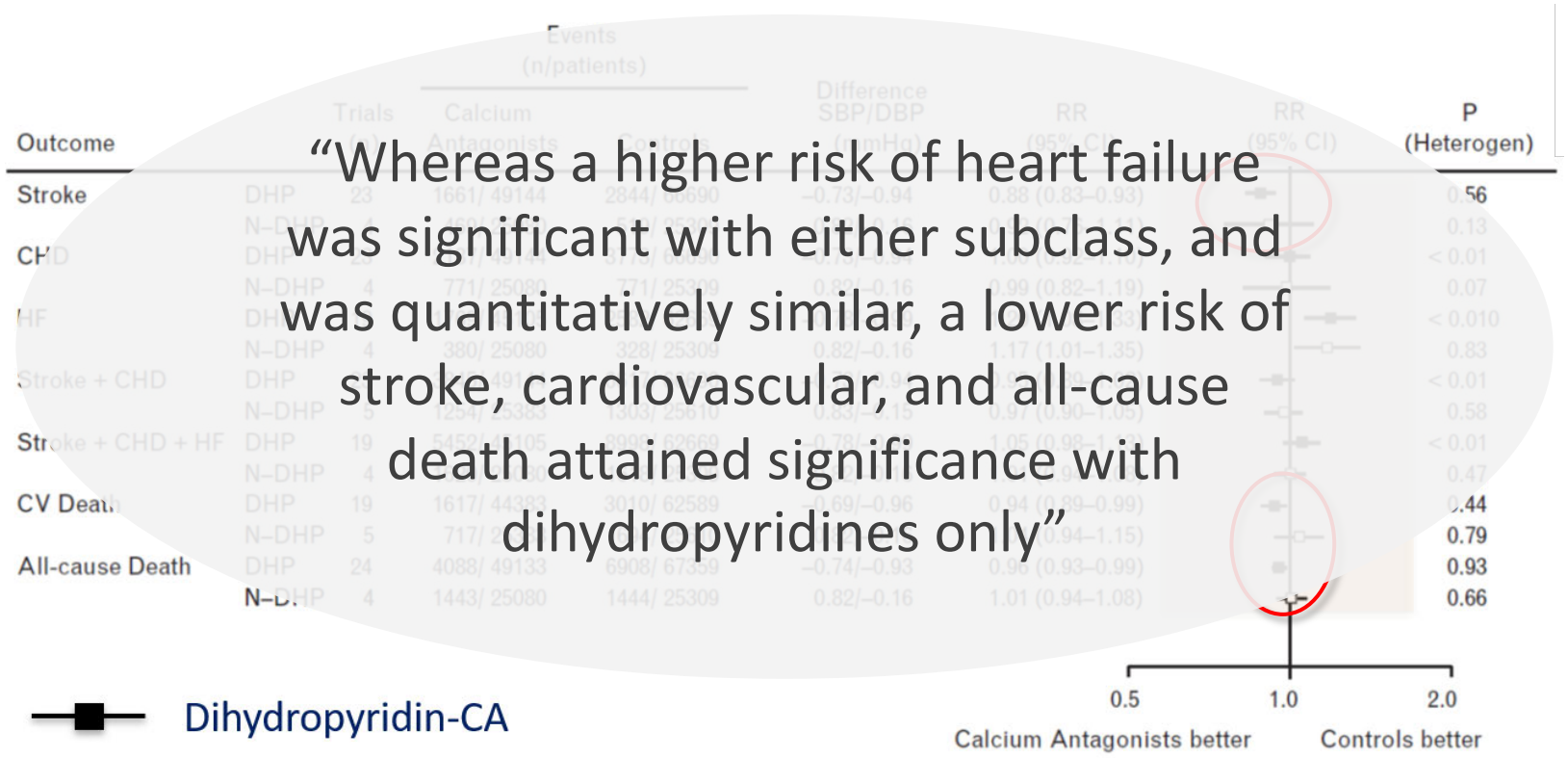
Dihydropyridin-CA

Nicht-Dihydropyridin-CA

Thomopoulos et al., J Hypertens 2015, 33:1321

Wirksamkeit von Calciumantagonisten vs. alle anderen in Studien eingesetzten Antihypertensiva

Separate Analyse für Dihydropyridin-CA (vorwiegend Amlodipin) und Nicht-Dihydropyridin-CA (Verapamil und Diltiazem)

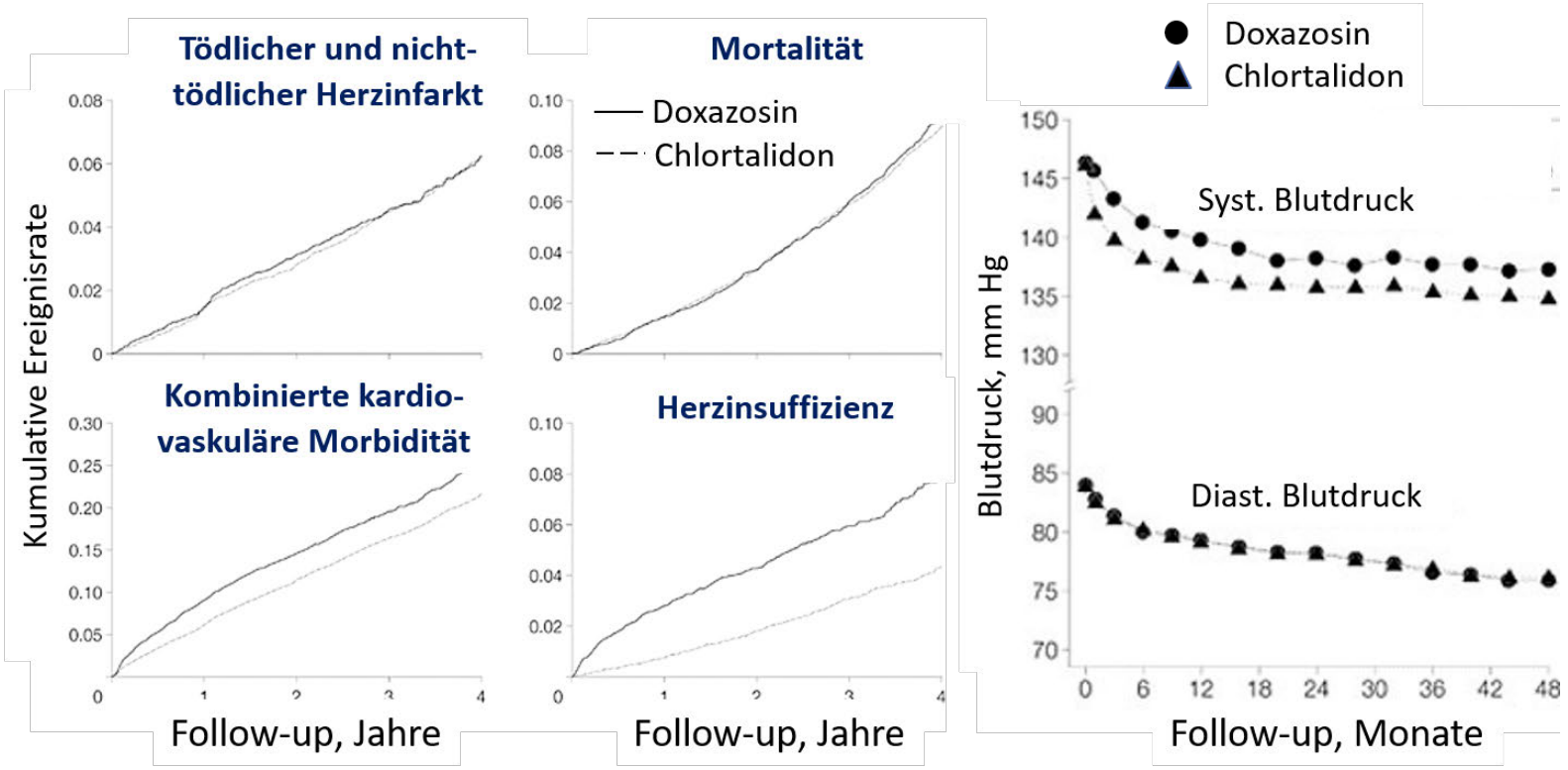


"Whereas a higher risk of heart failure was significant with either subclass, and was quantitatively similar, a lower risk of stroke, cardiovascular, and all-cause death attained significance with dihydropyridines only"

Thomopoulos et al., J Hypertens 2015, 33:1321

Doxazosin vs. Chlortalidon in ALLHAT*

24.335 Patienten ≥ 55 Jahre (15.268 Chlortalidon 12,5−25 mg/d; 9067 Doxazosin, 2−8 mg/d)
Vorzeitiger Abbruch der Studie nach 3,3 Jahren (Dezember 1999)



*The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

JAMA 2000; 293: 1967-1975

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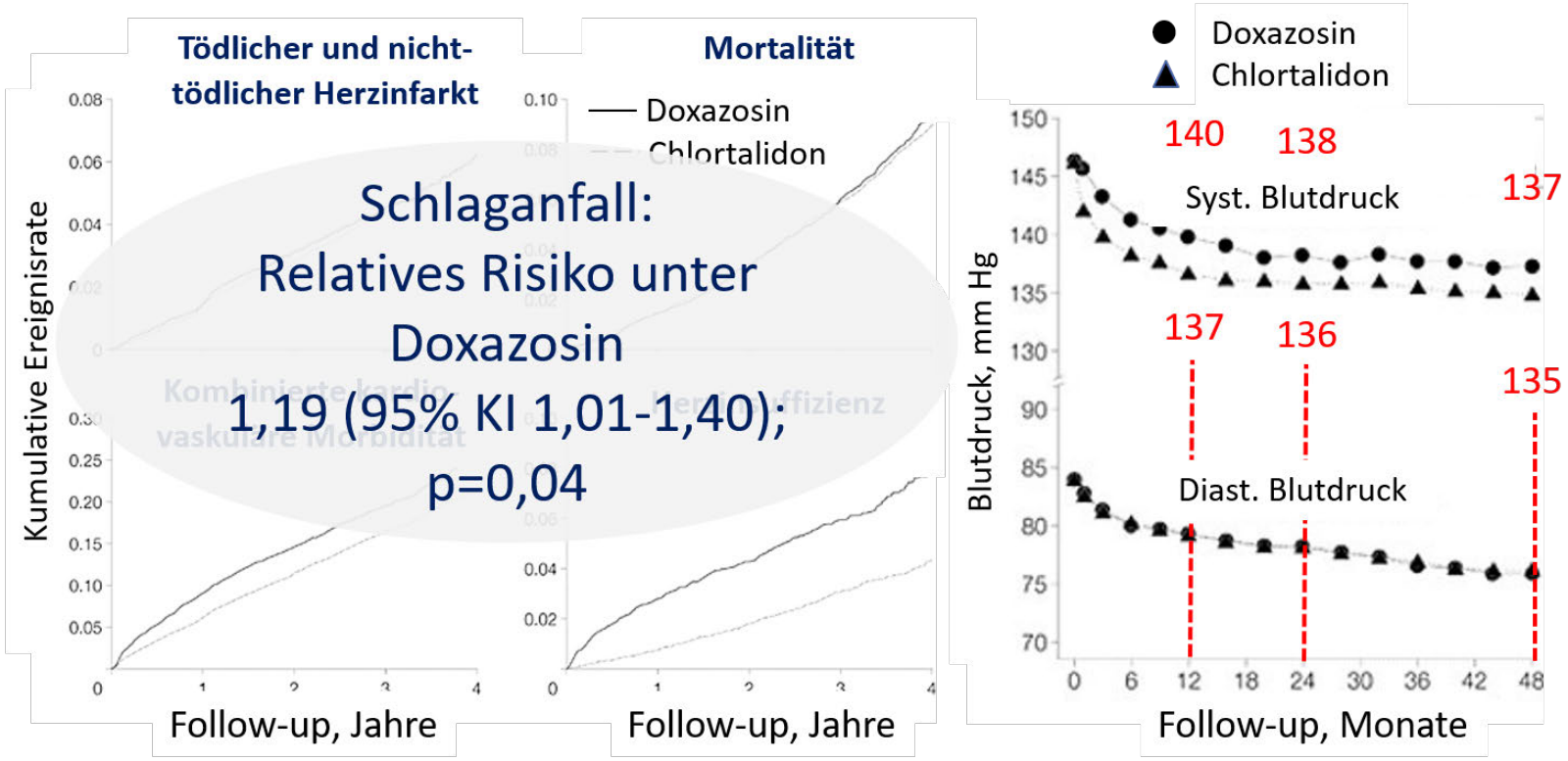

*The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

JAMA 2000; 293: 1967-1975

Fetal outcome in trial of antihypertensive treatment in pregnancy

The Lancet · Saturday 9 October 1976

FETAL OUTCOME IN TRIAL OF ANTIHYPERTENSIVE TREATMENT IN PREGNANCY

C. W. G. REDMAN

Nuffield Department of Obstetrics and Gynæcology, John Radcliffe Hospital, Headington, Oxford OX3 9DU

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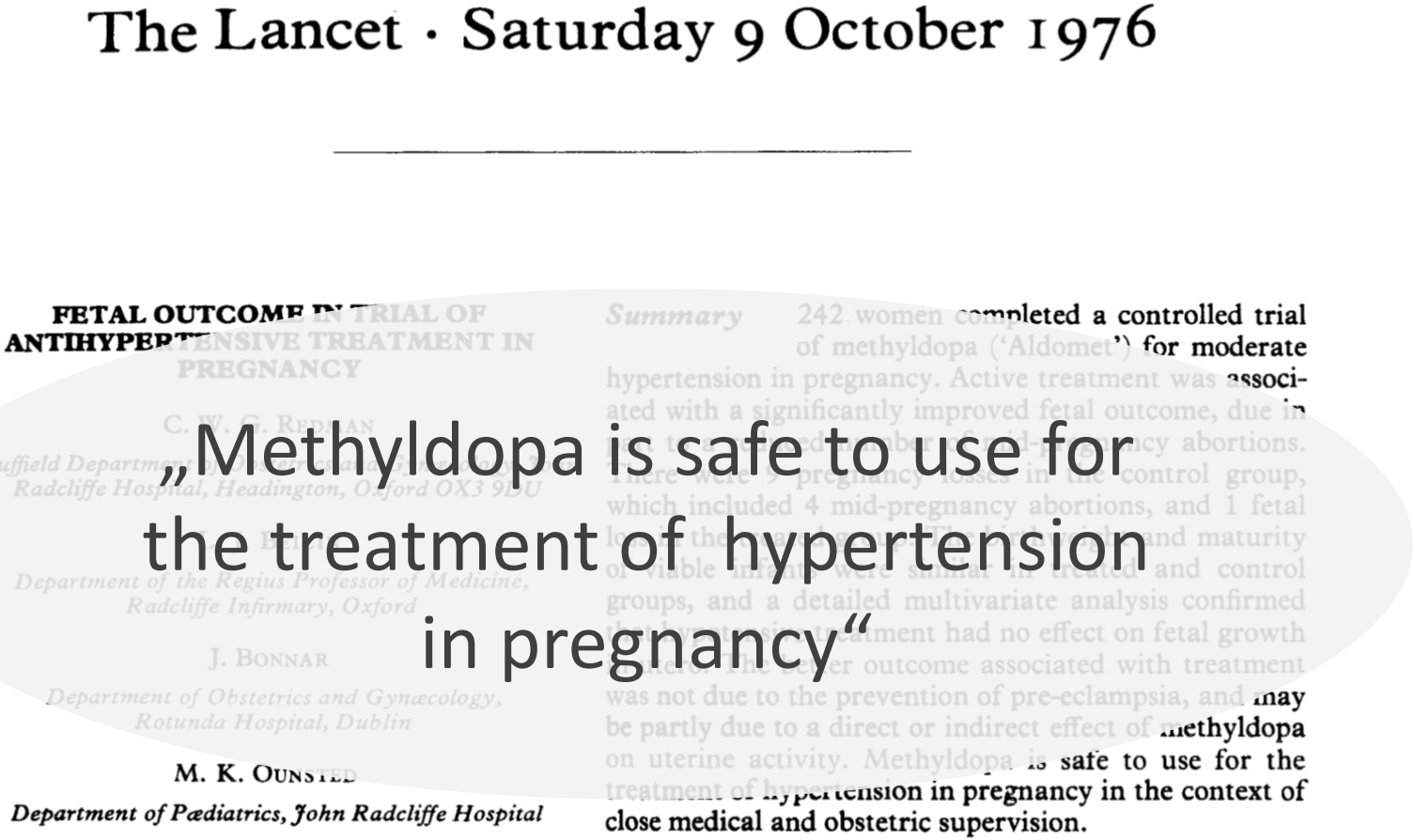
Department of Obstetrics and Gynæcology, Rotunda Hospital, Dublin

M. K. OUNSTED

Department of Pædiatrics, John Radcliffe Hospital

Summary 242 women completed a controlled trial of methyldopa ('Aldomet') for moderate hypertension in pregnancy. Active treatment was associated with a significantly improved fetal outcome, due in part to a reduced number of mid-pregnancy abortions. There were 9 pregnancy losses in the control group, which included 4 mid-pregnancy abortions, and 1 fetal loss in the treated group. The birthweight and maturity of viable infants were similar in treated and control groups, and a detailed multivariate analysis confirmed that hypotensive treatment had no effect on fetal growth in utero. The better outcome associated with treatment was not due to the prevention of pre-eclampsia, and may be partly due to a direct or indirect effect of methyldopa on uterine activity. Methyldopa is safe to use for the treatment of hypertension in pregnancy in the context of close medical and obstetric supervision.

Fetal outcome in trial of hypertensive treatment in pregnancy



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Summary 242 women completed a controlled trial of methyldopa ('Aldomet') for moderate hypertension in pregnancy. Active treatment was associated with a significantly improved fetal outcome, due in part to reduced perinatal loss and fewer mid-pregnancy abortions. There were 5 pregnancy losses in the control group, which included 4 mid-pregnancy abortions, and 1 fetal loss in the treated group. Birthweight and maturity of viable infants were similar in treated and control groups, and a detailed multivariate analysis confirmed that hypertensive treatment had no effect on fetal growth retardation. The better outcome associated with treatment was not due to the prevention of pre-eclampsia, and may be partly due to a direct or indirect effect of methyldopa on uterine activity. Methyldopa is safe to use for the treatment of hypertension in pregnancy in the context of close medical and obstetric supervision.

„Methyldopa is safe to use for the treatment of hypertension in pregnancy“

Clonidin (und Moxonidin)

Wirkungsmechanismus

- Aktivierung prä-und postsynaptischer α2-Adrenozeptoren (zentral und peripher)
- Zusätzlich Stimulation von so genannten Imidazolin-Rezeptoren (ZNS)
- Schwache agonistische Wirkung auf periphere α1-Adrenozeptoren (Cave Blutdruckanstieg bei schneller i.v. Gabe)

Pharmakologie

- Kurze Wirkdauer, daher Mehrfachgabe (pro Tag) notwendig. Retardpräparat bei hoher Dosierung (Clonidin ret. 250 µg) verfügbar

Indikationen

- Hypertonie (hypertensive Krise, Therapie-refraktäre Hypertonie, Hypertonie bei fortgeschrittener Niereninsuffizienz)
- Alkoholentzug, Migräneprophylaxe, Menstruationsbeschwerden, Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung ADHS

Nebenwirkungen

- Trockener Mund, Bradykardie, orthostatische Störungen, erektile Dysfunktion, Blutdruckanstieg bei plötzlichem Absetzen

Clonidin (und Moxonidin)

Wirkungsmechanismus

-
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Ne

- Trockener Mund, Bradykardie, orthostatische Störungen, erektile Dysfunktion, Blutdruckanstieg bei plötzlichem Absetzen

Moxonidin

- Längere Wirkdauer (Einmalgabe), schwächere Hauptwirkung und Nebenwirkungen
- Postuliert wird eine schwächere Wirkung an α2-Rezeptoren verbunden mit einer stärkeren Wirkung auf Imidazolinrezeptoren
- Keine „Endpunktstudien“ bei Hypertonie
- Endpunktstudie bei Herzinsuffizienz (MOXCON) mit erhöhter Morbidität und Mortalität[1]

[1]Cohn et al., Eur J Heart Fail. 2003;5:659

Zusammenfassung (1)

- RAS-Blocker (ACE-Hemmer und Angiotensin-Rezeptorantagonisten), Calciumantagonisten und Diuretika sind die primär einzusetzenden Antihypertensiva
- ß-Blocker sind in Interventionsstudien (alle mit „klassischen“ ß-Blockern, überwiegend Atenolol, durchgeführt) bezüglich der Prävention insbesondere cerebrovaskulärer Komplikationen den meisten anderen Antihypertensiva unterlegen
- Mögliche Ursachen der schwächeren Wirksamkeit von ß-Blockern
  - Schlechte Adhärenz
  - metabolische Nebenwirkungen, z.B. diabetogene Wirkung
  - schwächere Absenkung des „zentralen“ Blutdrucks
- ß-Blocker = heterogene Substanzgruppe, wobei vasodilatierende ß-Blocker (insbesondere Nebivolol) bezüglich Adhärenz, Verträglichkeit und „zentraler“ Blutdrucksenkung besser abschneiden

Zusammenfassung (2)

- Spironolacton oder anderes Diuretikum Substanzen der Wahl bei Therapieresistenz
- Wirkverlust von Thiaziden und Thiazid-artigen Diuretika bei eingeschränkter Nierenfunktion. Ab chronischer Nierenerkrankung (CKD) Stadium IV daher Präferenz bei Schleifendiuretika
- Insgesamt „schwache“ Studienlage für Schleifendiuretika bei Hypertonie
- Nicht-Dihydropyridin Calciumantagonisten (Verapamil, Diltiazem) mit schlechterer Blutdrucksenkung und Prognoseverbesserung als Dihydropyridine (z.B. Amlodipin)
- α1-Rezeptorenblocker durch ALLHAT zu schlecht bewertet. Weniger Ödeme als unter Calciumantagonisten. Günstige Zusatzwirkung bei benigner Prostatahypertrophie
- Antisympathotonika bei Schwangerschaft (Methyldopa), Alkoholismus (Clonidin) und Therapieresistenz

Kontakt

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Vielen Dank für Ihre Aufmerksamkeit!