Treatment of arterial hypertension in 2010

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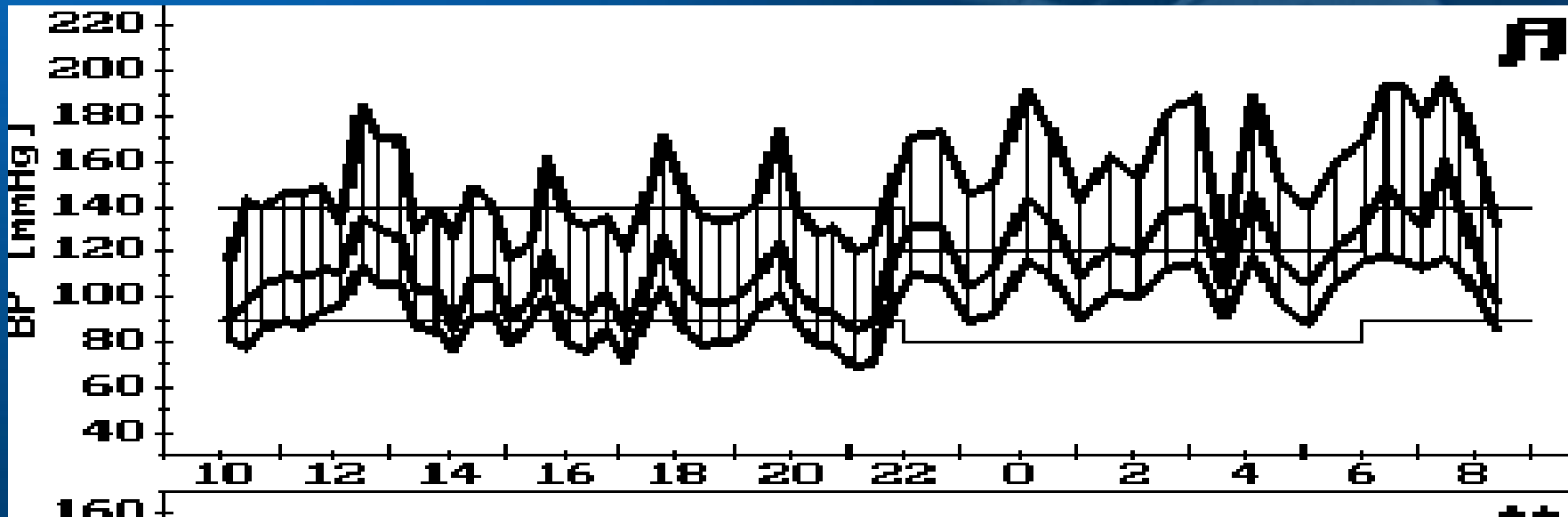
Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document

Journal of Hypertension 2009

Treatment of arterial hypertension in 2010

- Variability of blood pressure
- Target blood pressure levels
- Novel approaches to nonpharmacological treatment
- Combination of antihypertensive drugs
- New type of antihypertensive agents

BP variability as a risk factor for CV disease/complications?

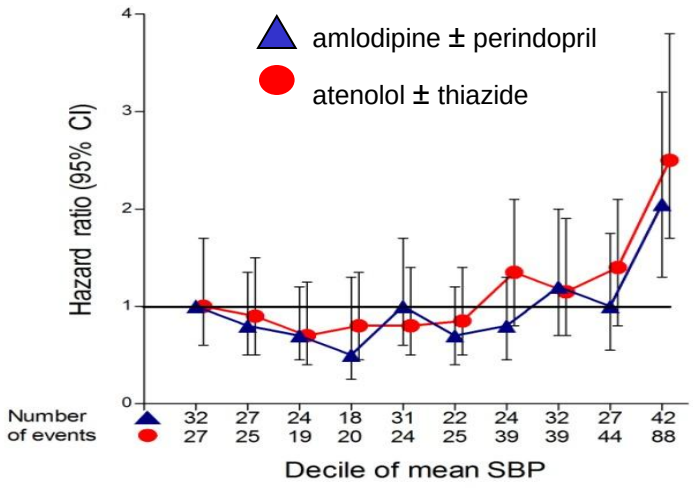
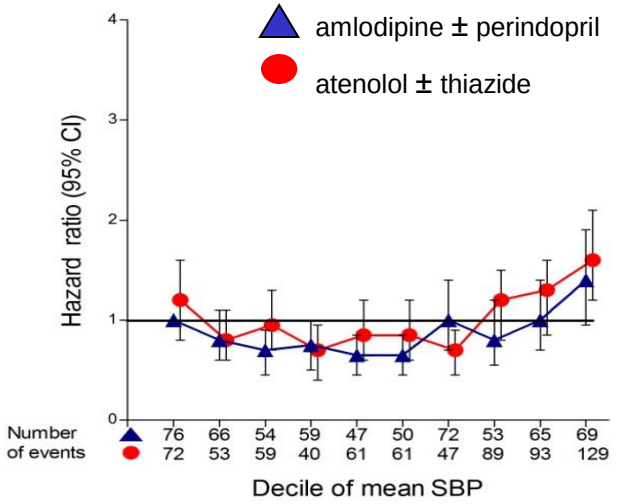
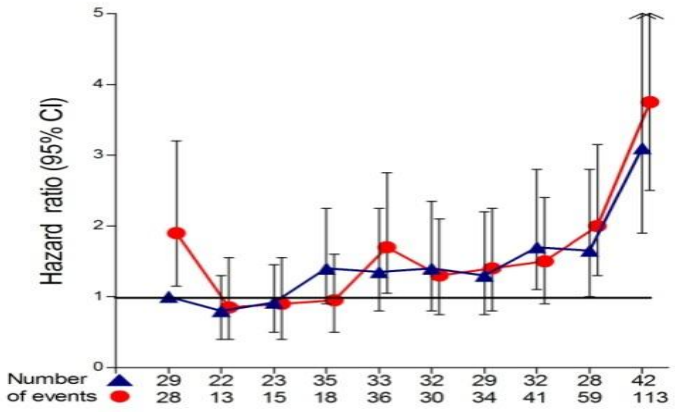
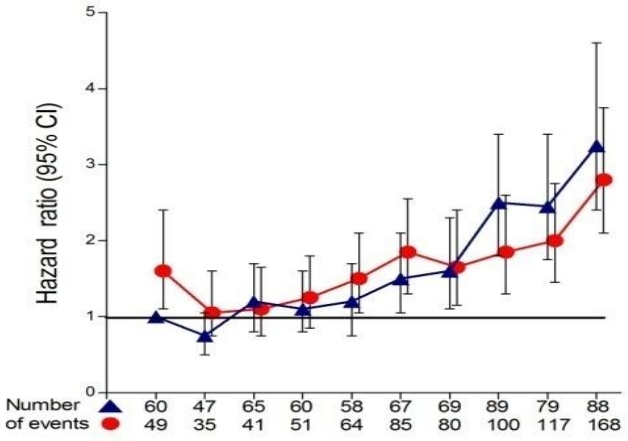


Blood Pressure Variability: Methods

- Visit-to-visit variability of SBP and DBP during follow-up, from 6 months after randomisation to the end of the trial, expressed as standard deviation (SD), coefficient of variation (CV), and variability independent of mean – (VIM)
- Within-visit variability expressed as SD of the three measurements taken at each visit averaged across all follow-up visits
- Among 1905 patients, mean BP and variability were also determined with annual 24 hour ambulatory monitoring (ABPM)
- Cox models were used to determine associations with risks of vascular events during follow-up, and whether an effect on variability in BP could account for the reduction in events in the amlodipine/perindopril group

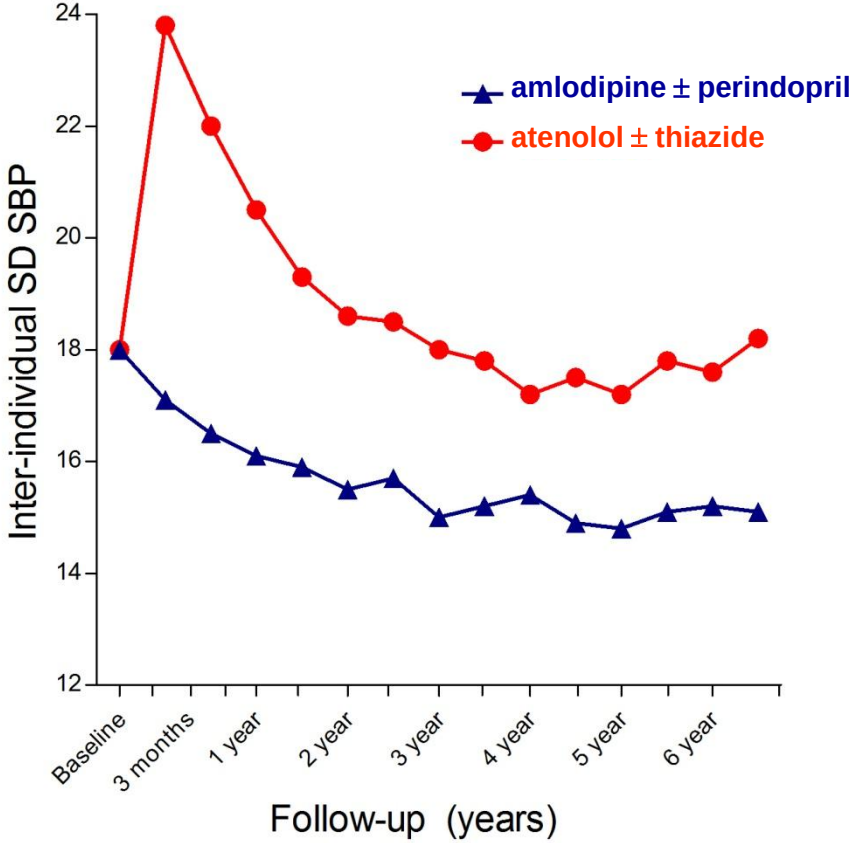
ascot

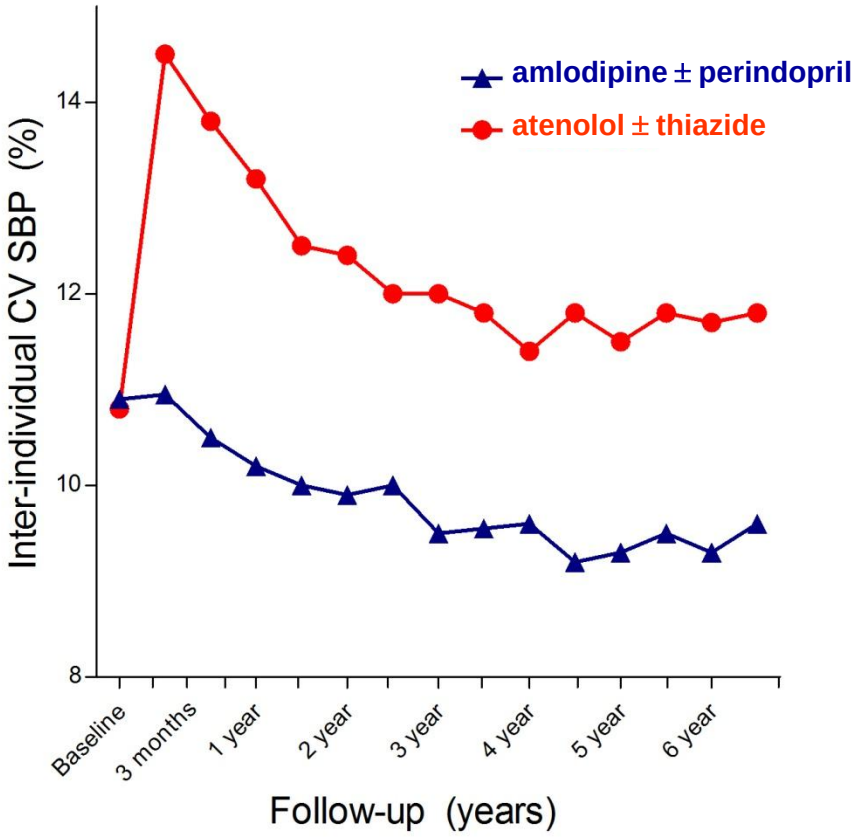
Mean SBP Variability of SBP and Risk of Stroke and CHD in ASCOT-BPLA

	Stroke	CHD
Mean SBP		
Coefficient of variation in SBP		

Rothwell PM, *et al. Lancet*. 2010;375:895-905.

Group distribution (SD and CV) of measures of SBP at baseline and at each follow-up visit in the two treatment groups





Impact of Amlodipine/Perindopril vs Atenolol/Thiazide on Stroke and CHD Risk Adjusting for BP Variables

	Stroke		CHD	
Adjustment Variables	**HR**	**P**	**HR**	**P**
Treatment (℞)	0.78	0.001	0.85	0.002
℞ + Mean SBP	0.84	0.025	0.88	0.019
℞ + Mean SBP + CV SBP	0.95	0.55	1.00	0.98
℞ + Mean SBP + CV SBP + WVSD SBP	0.99	0.89	1.01	0.88

BP variability- summary: ASCOT

- Various measures of visit-to-visit BP variability (SD, coefficient of variation and variation independent of mean BP) are powerful predictors of both stroke and CHD outcomes
- Variability increased with age, diabetes, smoking, and in those with established vascular disease
- Other measures of variability (within-visit variability and variability assessed by ABPM) also predict cardiovascular outcomes but less than visit-to-visit variability
- Amlodipine/perindopril reduces blood pressure variability compared with atenolol/thiazide
- Adjusting for BP variability completely explains differences in stroke and CHD outcomes between amlodipine/perindopril and atenolol/thiazide treatment in ASCOT

ascot

Summary: BP variability

- **Potential differences among antihypertensive classes? (CCB as the most powerful class of drugs?)**
- **Potential differences between various combinations? e.g. ASCOT trial (amlodipin/perindopril vs. atenolol/thiazides)**
- **Adequate BP control remain priority !!**

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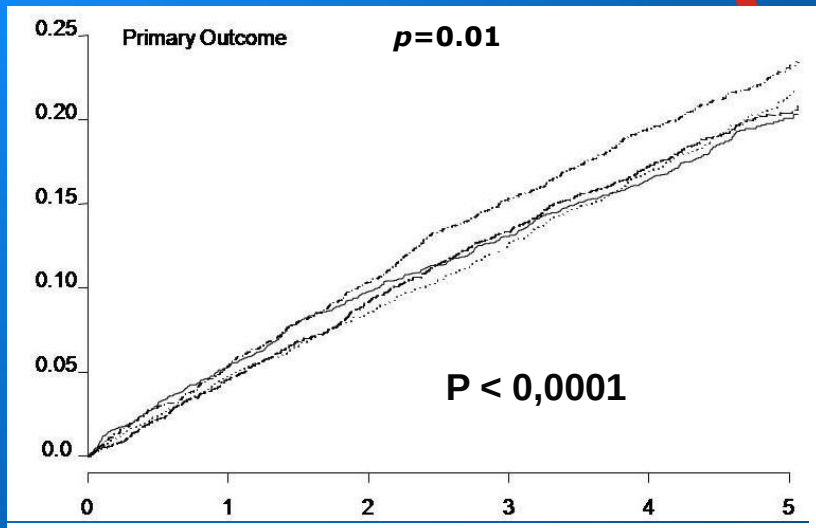
Goals of Treatment

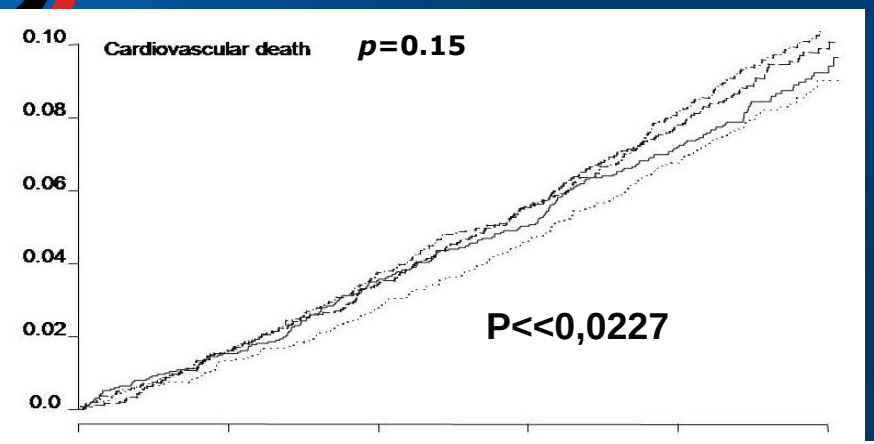
- In hypertensive patients, the primary goal of treatment is to achieve maximum reduction in the long-term total risk of cardiovascular disease.
- This requires treatment of the raised BP per se as well as of all associated reversible risk factors.
- BP should be reduces to at least below 140/90 mmHg (systolic/diastolic) and to lower values, if tolerated, in all hypertensive patients.

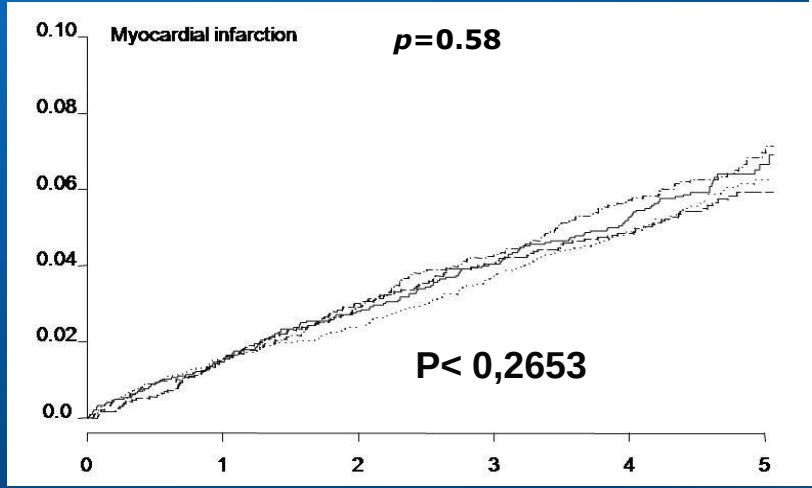
Goals of Treatment

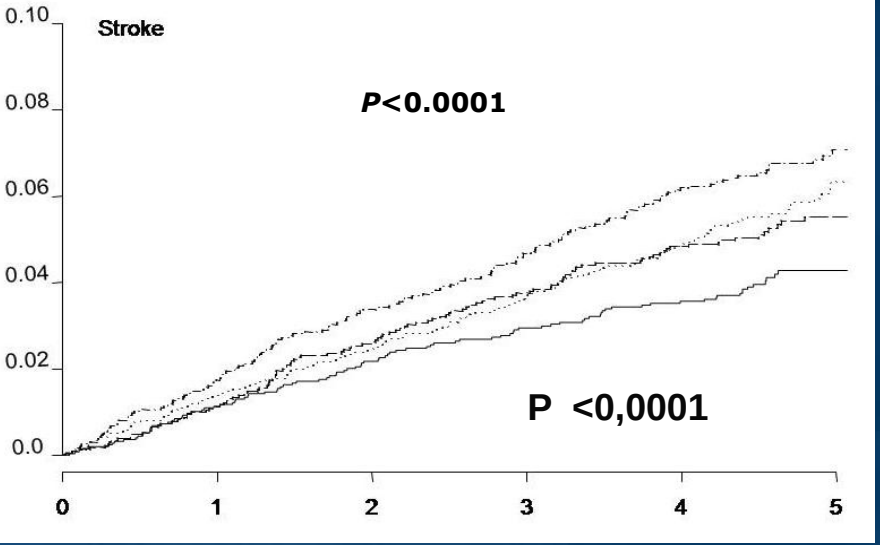
- Target BP should be at least <130/80 mmHg in diabetics and in high or very high risk patients, such as those with associated clinical conditions (stroke, myocardial infarction, renal dysfunction, proteinuria), evidence ???
- Despite use of combination treatment, reducing systolic BP to <140 mmHg may be difficult and more so if the target is a reduction to <130 mmHg. Additional difficulties should be expected in elderly and diabetic patients and, in general, in patients with cardiovascular damage.
- In order to more easily achieve goal BP, antihypertensive treatment should be initiated before significant cardiovascular damage develops.

Prognostic value of BP: ONTARGET





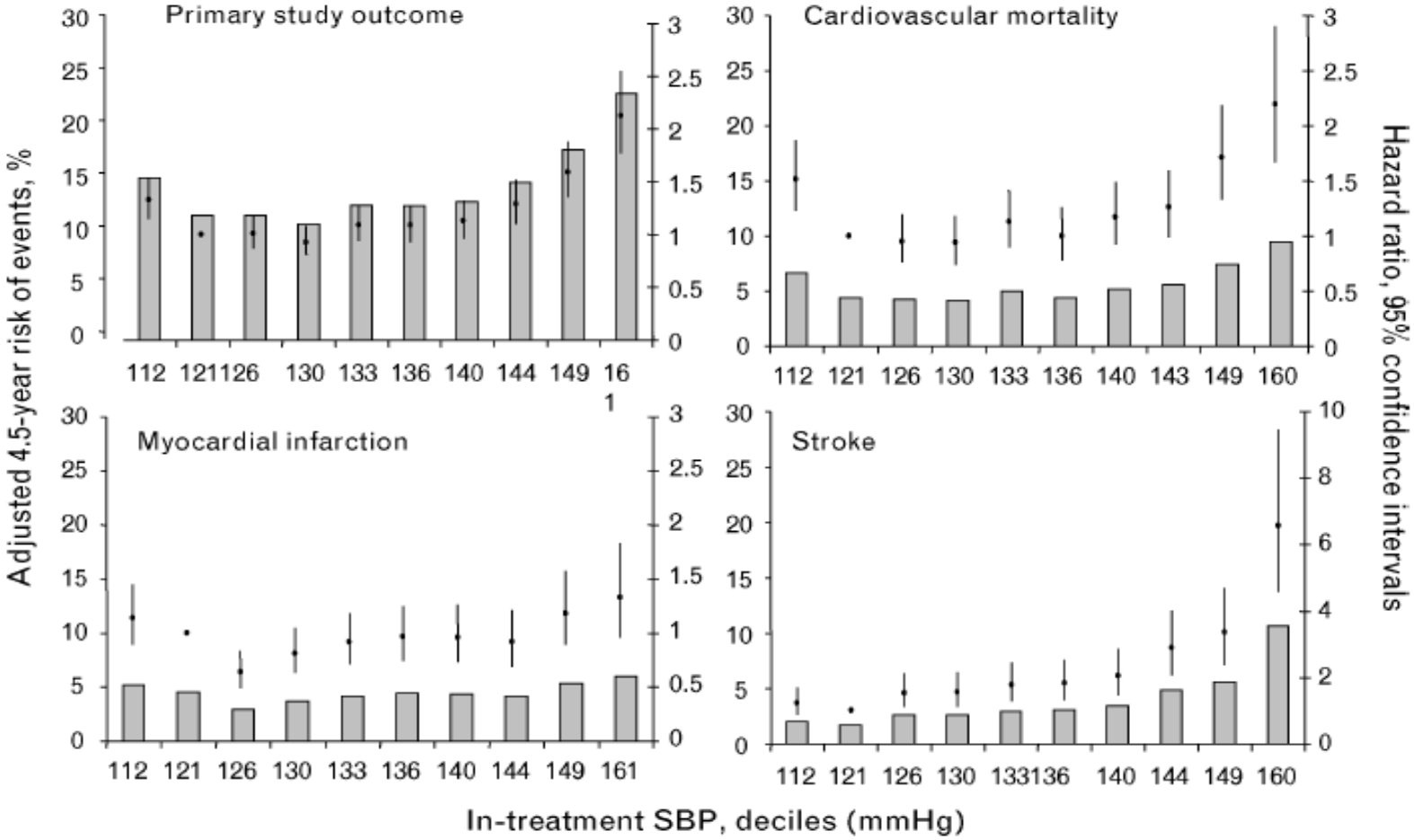




Q1 <132 mmHg; Q2 132-144 mmHg; Q3 144-155 mmHg; Q4 >155 mmHg

Sleight P, et al. J Hypertens. 2009; 27:1360–1369

Prognostic value of BP:ONTARGET



Sleight P, et al. J Hypertens. 2009; 27:1360–1369.

Effects of Intensive Blood Pressure Control on Cardiovascular Events in Type 2 Diabetes Mellitus: The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure Trial

William C. Cushman, MD, FACP, FAHA

Veterans Affairs Medical Center, Memphis, TN

For The ACCORD Study Group

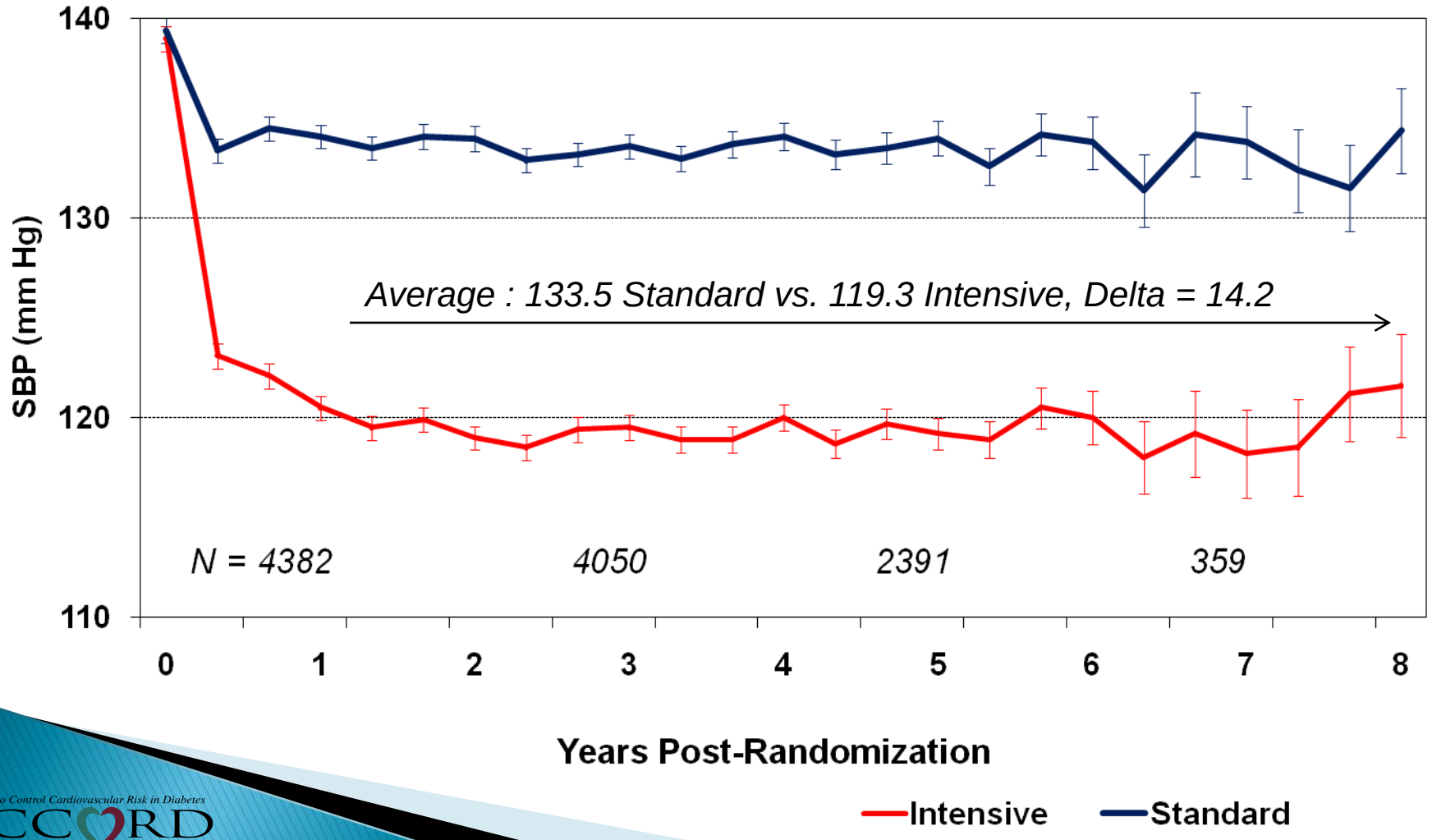
Action to Control Cardiovascular Risk in Diabetes

ACCORD

Systolic Pressures (mean ± 95% CI)

Mean # Meds

Intensive:	*3.2*	*3.4*	*3.5*	*3.4*
Standard:	*1.9*	*2.1*	*2.2*	*2.3*



Action to Control Cardiovascular Risk in Diabetes
ACCORD

Primary & Secondary Outcomes

	Intensive Events (%/yr)	Standard Events (%/yr)	HR (95% CI)	P
Primary	208 (1.87)	237 (2.09)	0.89 (0.73-1.07)	0.20
Total Mortality	150 (1.28)	144 (1.19)	1.07 (0.85-1.35)	0.55
Cardiovascular Deaths	60 (0.52)	58 (0.49)	1.06 (0.74-1.52)	0.74
Nonfatal MI	126 (1.13)	146 (1.28)	0.87 (0.68-1.10)	0.25
Nonfatal Stroke	34 (0.30)	55 (0.47)	0.63 (0.41-0.97)	0.03
Total Stroke	36 (0.32)	62 (0.53)	0.59 (0.39-0.89)	0.01

Also examined Fatal/Nonfatal HF (HR=0.94, p=0.67), a composite of fatal coronary events, nonfatal MI and unstable angina (HR=0.94, p=0.50) and a composite of the primary outcome, revascularization and unstable angina (HR=0.95, p=0.40)

Adverse Events

	Intensive N (%)	Standard N (%)	P
Serious AE	77 (3.3)	30 (1.3)	<0.0001
Hypotension	17 (0.7)	1 (0.04)	<0.0001
Syncope	12 (0.5)	5 (0.2)	0.10
Bradycardia or Arrhythmia	12 (0.5)	3 (0.1)	0.02
Hyperkalemia	9 (0.4)	1 (0.04)	0.01
Renal Failure	5 (0.2)	1 (0.04)	0.12
eGFR ever <30 mL/min/1.73m^2	99 (4.2)	52 (2.2)	<0.001
Any Dialysis or ESRD	59 (1.2)	58 (1.2)	0.91
Dizziness on Standing†	217 (44)	188 (41)	0.39

† Symptom experienced over past 30 days from HRQL sample of N=943 participants assessed at 12 and 48 months post-randomization

Conclusions:

- In patients with high CV risk is benefit of SBP lowering below 130 mmHg associated with decreased risk of stroke
- Lowering of SBP below 130 mmHg does not influence the risk of MI and total CV mortality /CV mortality may even increase/
- Clinical benefit of SBP lowering below 130 mmHg is uncertain

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Novel approaches to nonpharmacological treatment of resistant hypertension

- Carotid baroreceptor stimulation-implantable device
- Renal sympathetic denervation

Prevalence of resistant hypertension:

- 5 % in general population
- 5-20 % in specialized centers
- 10% in our center in Prague

CONVINCE:

- 1 year : 30% uncontrolled
- → 38% : ≥ 3 AHT agents

HOT:

8.5 % : >140/90 mmHg

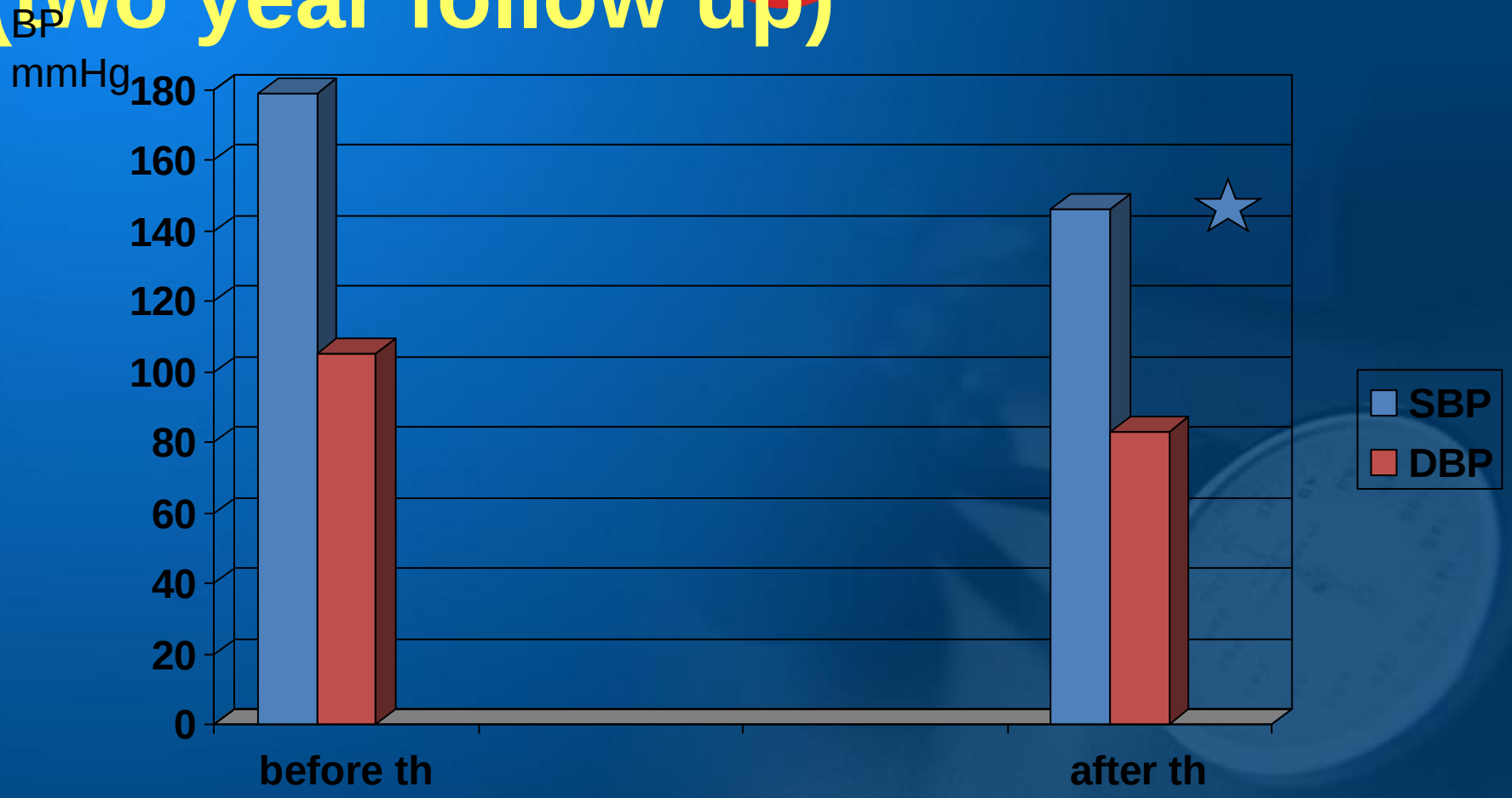
ALLHAT:

- 1 year : 47% of 14722 pts: >140/90 mmHg

Syst-Eur : 43% : >150 mmHg

LIFE : 74% : >140 mmHg

CB stimulation: Results of multicenter Europe feasibility study (two year follow up)



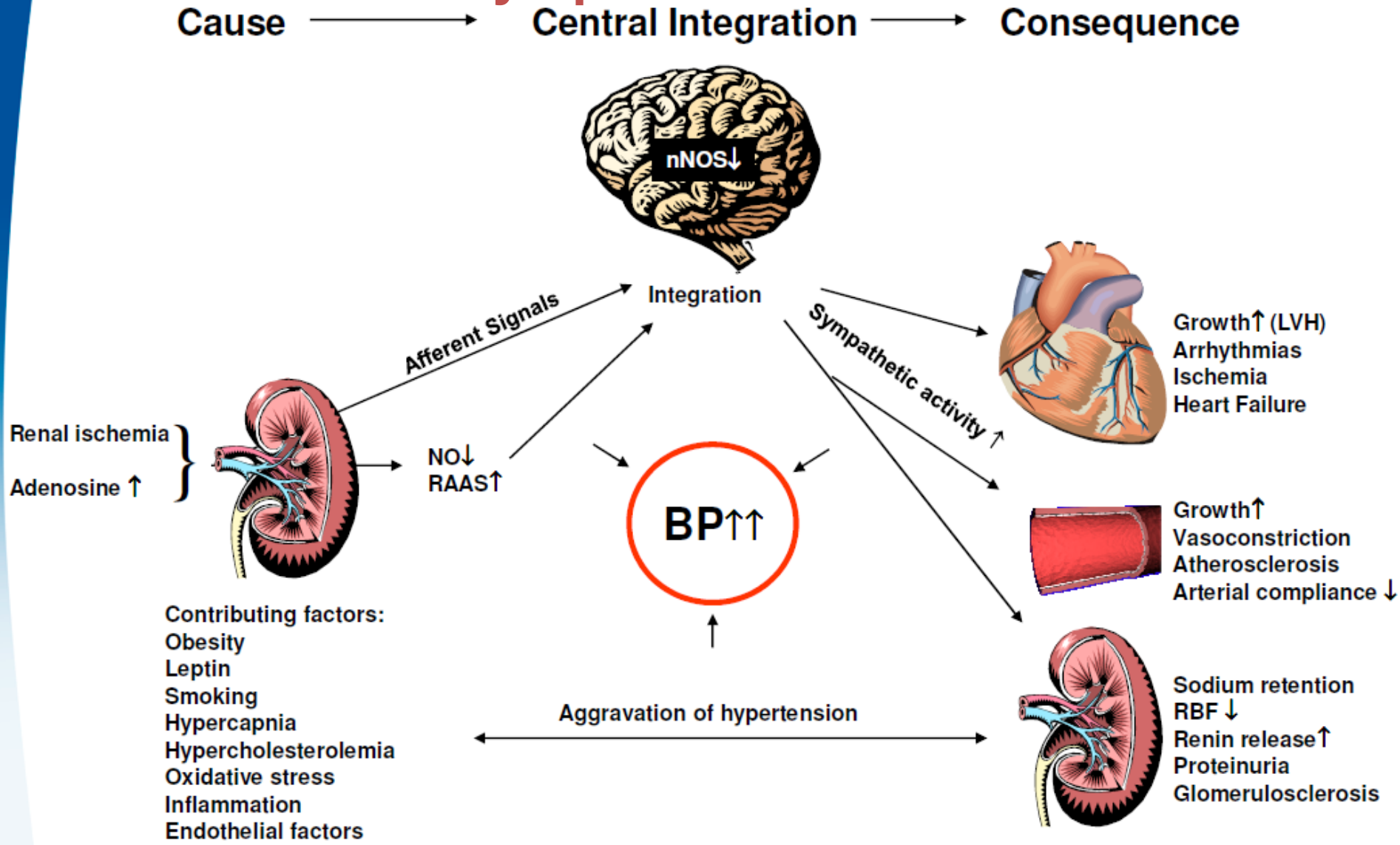
★ P ≤0,05

J Am. Coll. Card., 2010, 56, 1254-1258

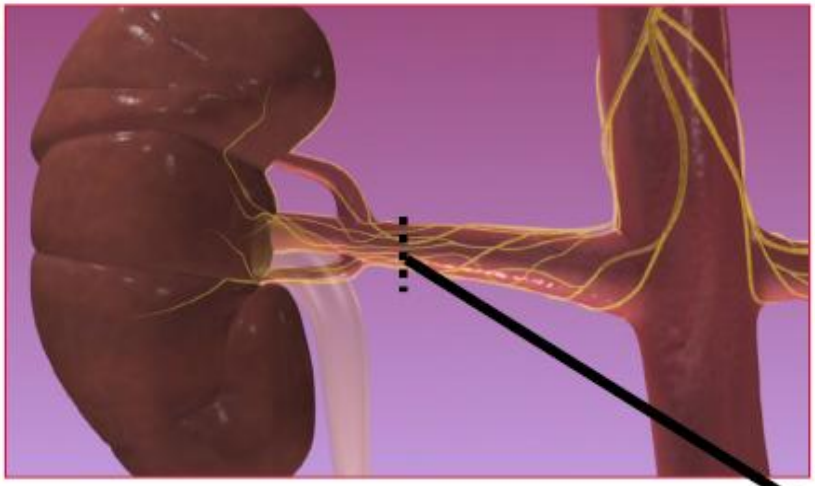
Carotid baroreceptor activation therapy in resistant hypertension: problems

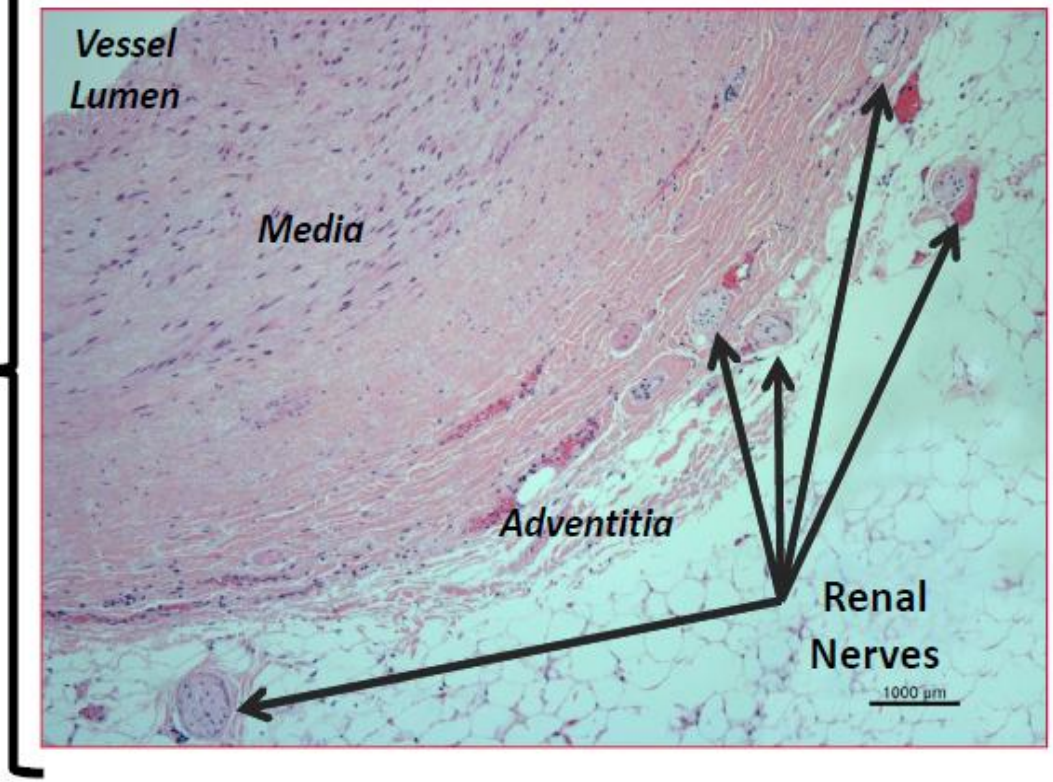
- Low number of subjects who completed two year follow up
- Not all patients responded by BP decrease
- Relatively frequent complications- local bleeding, inflammation etc.
- Invasive procedure
- Costs??

Renal sympathetic denervation



Renal Anatomy Allows a Catheter-Based Approach





- Arise from T10-L2
- Follow the renal artery to the kidney
- Primarily lie within the adventitia
- The only location that renal efferent & afferent nerves travel together

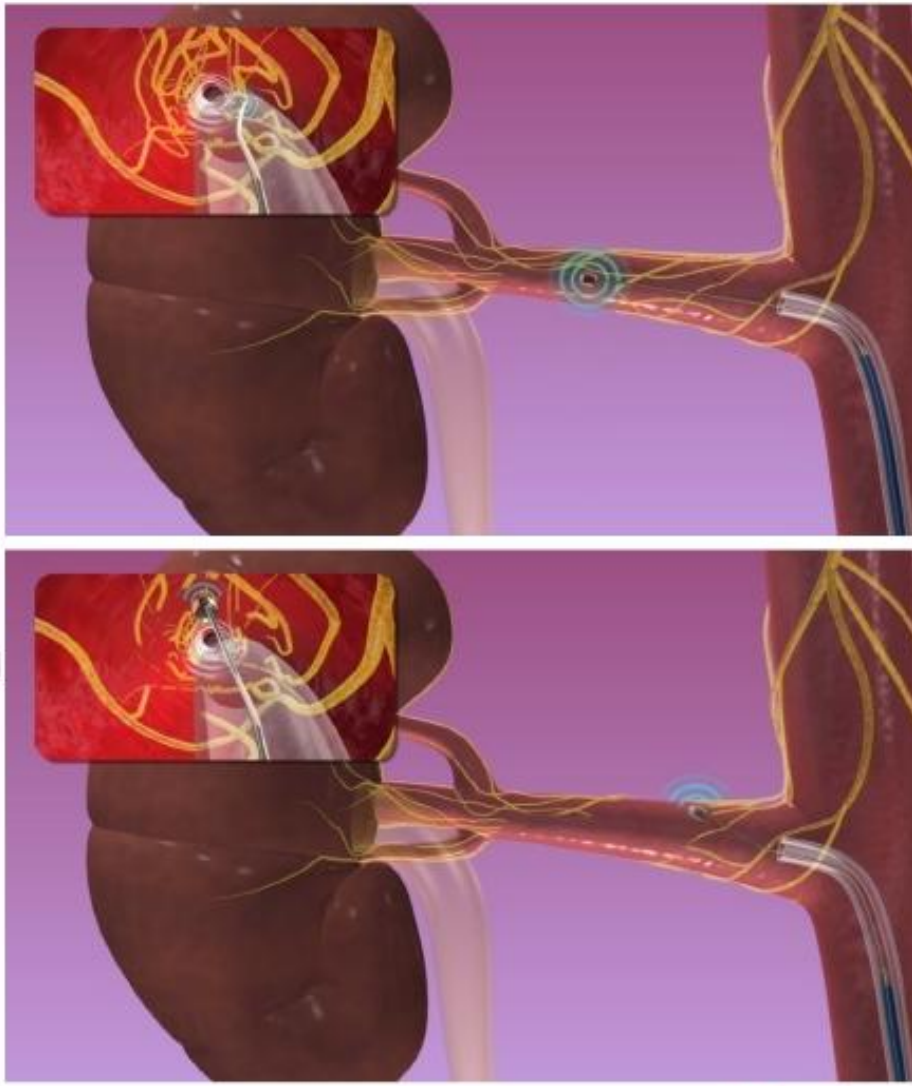
Baker IDI

Catheter-Based Treatment for Achieving Renal Sympathetic Denervation

Symplicity® Catheter System™
Ardian, Inc., Palo Alto, CA, USA

- 6F access
- Articulating tip with RF electrode

- Renal nerves lie in adventitia, encircling the renal arteries
- 4-6 focal 2-minute RF treatments along each renal artery



THE LANCET

Volume 373 · Number 9671 · Pages 1223-1310 · April 11-17, 2009 www.thelancet.com

Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study

Henry Krum, Markus Schlaich, Rob Whitbourn, Paul A Sobotka, Jerzy Sadowski, Krzysztof Bartus, Bogusław Kapelak, Anthony Walton, Horst Sievert, Suku Thambar, William T Abraham, Murray Esler

Lancet. 2009;373:1275-1281

Initial Cohort – Reported in the *Lancet*, 2009:

- First-in-man, non-randomized
- Cohort of 45 patients with resistant HTN (SBP ≥160 mmHg on ≥3 anti-HTN drugs, including a diuretic; eGFR ≥ 45 mL/min)
- 12-month data

Expanded Cohort – This Report:

- Expanded cohort of patients (n=153)
- 24-month follow-up

Chronic Safety

- No RF treatment related vascular complications
  - One progression of a pre-existing renal artery stenosis (40%→80%), possibly related to catheter manipulation, successfully stented
- Stable renal function (better than natural history)
  - 3 Month eGFR Δ: -0.7 ± 13.9 mL/min, p=0.65, n=83
  - 6 month eGFR Δ: -0.2 ± 13.6 mL/min, p=0.89, n=80
  - 12 Month eGFR Δ : -2.7 ± 12.9 mL/min, p=0.11, n=58
- No orthostatic hypotension
- No electrolyte disturbances
- Two deaths within the follow-up period; both unrelated to the device or therapy

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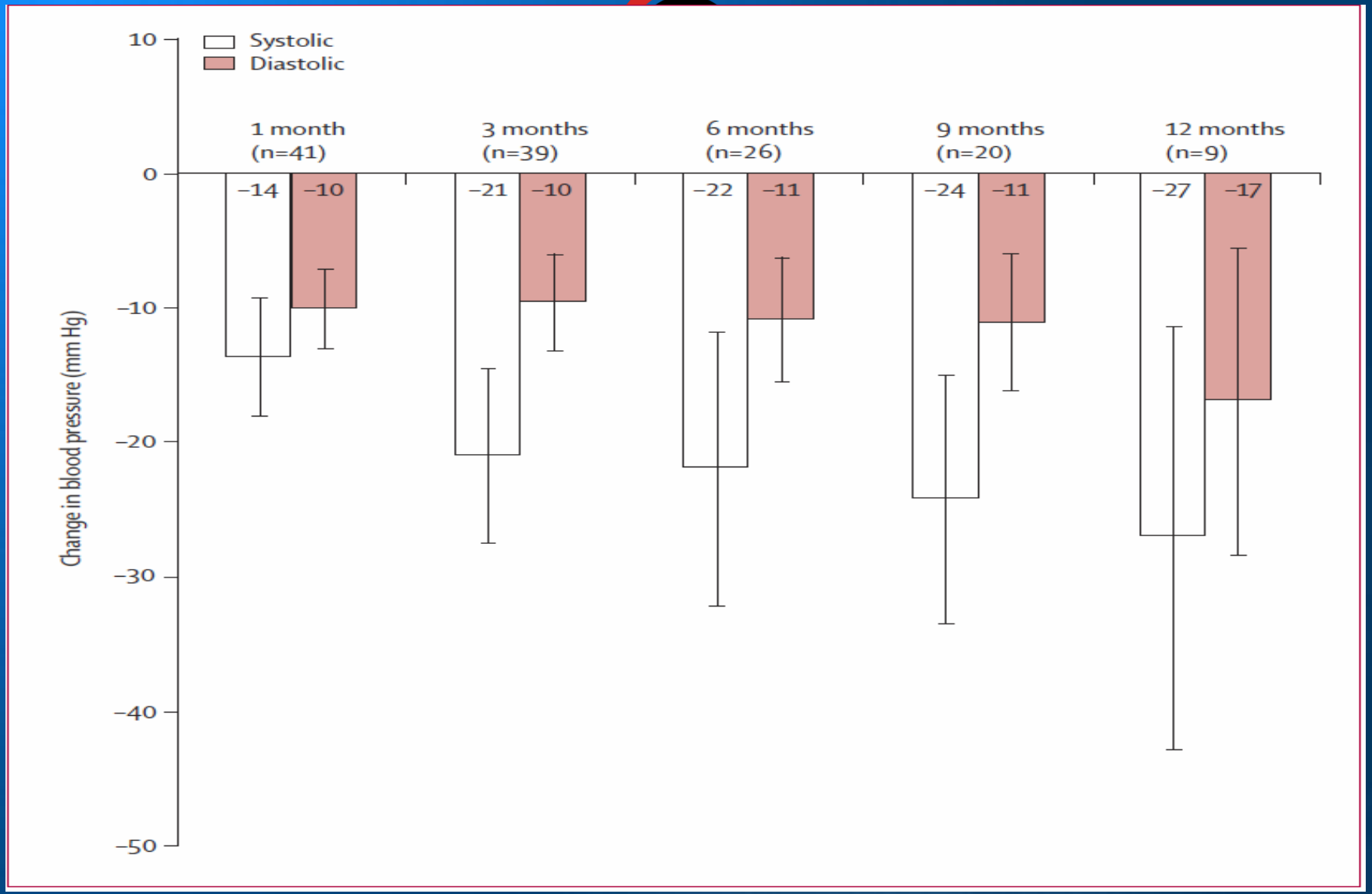
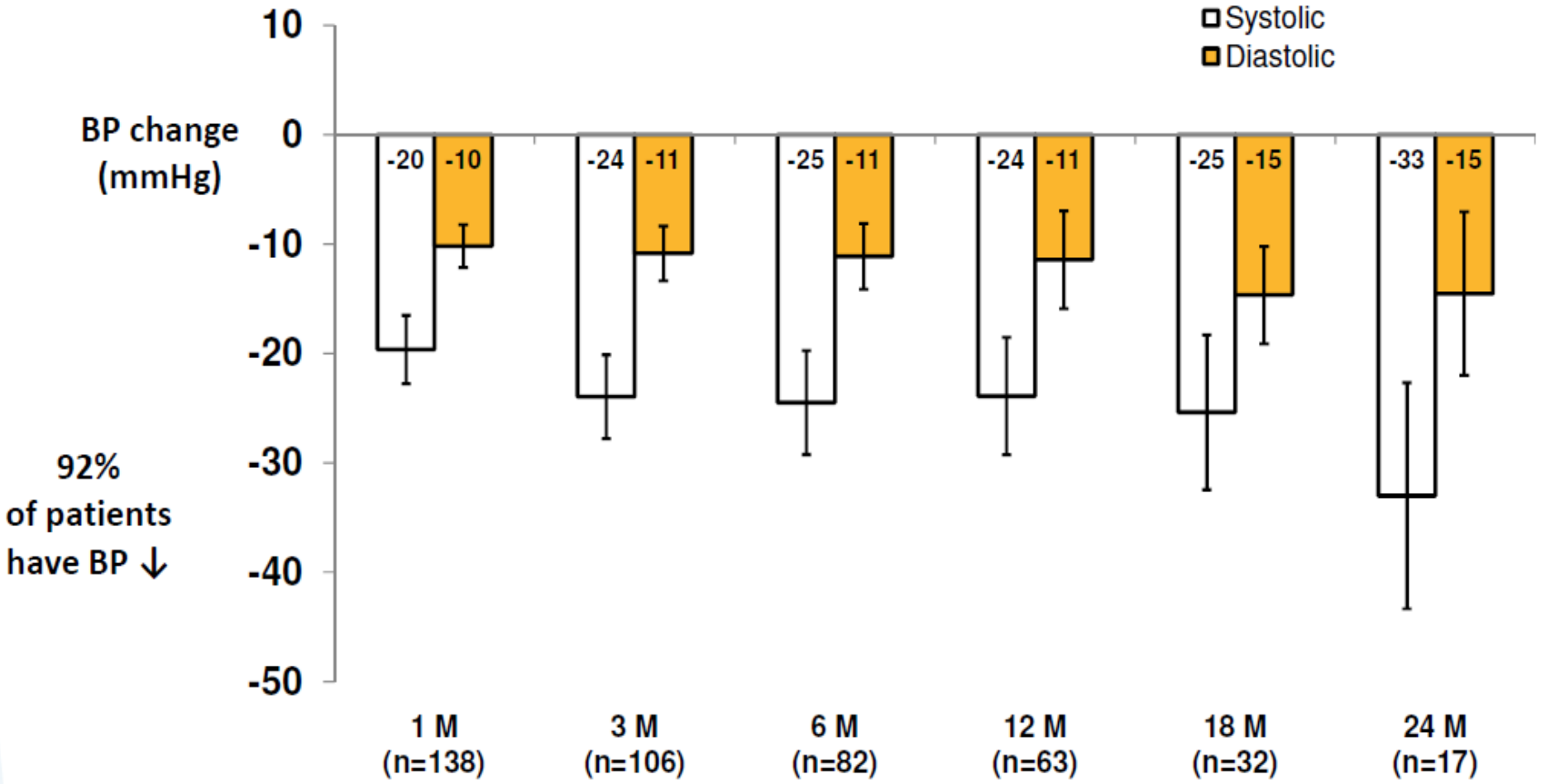
HEART & DIABETES INSTITUTE

Renal denervation: results after one year



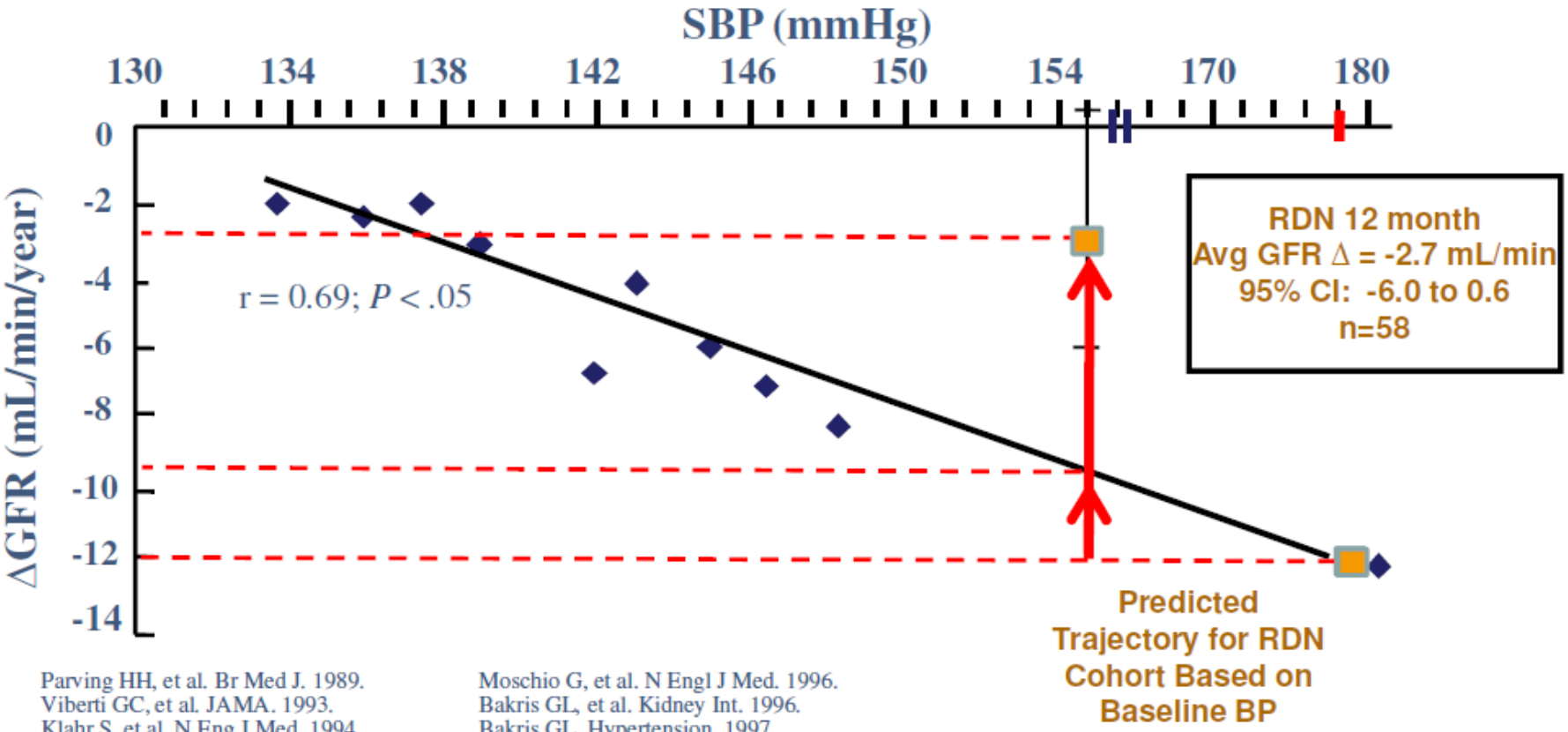
Lancet 2009, 373, 1275-81

Significant, Sustained BP Response



92% of patients have BP ↓

Renoprotection?



Parving HH, et al. Br Med J. 1989.
Viberti GC, et al. JAMA. 1993.
Klahr S, et al. N Eng J Med. 1994.
Hebert L, et al. Kidney Int. 1994.
Lebovitz H, et al. Kidney Int. 1994.

Moschio G, et al. N Engl J Med. 1996.
Bakris GL, et al. Kidney Int. 1996.
Bakris GL. Hypertension. 1997.
The GISEN Group. Lancet. 1997.

Bakris et al. Am J Kidney Dis. 2000;36(3):646-661

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Renal sympathetic denervation

- **Potentially promissing method with many unsolved issues:**
- **Heterogennic population of small group of subjects with resistant hypertension-secondary etiology?**
- **Compliance to therapy/modification of combination treatment?**
- **Only office BP values available**
- **Invasive character, econ. aspects**
- **Control group?**

„The results are too nice to be true?“

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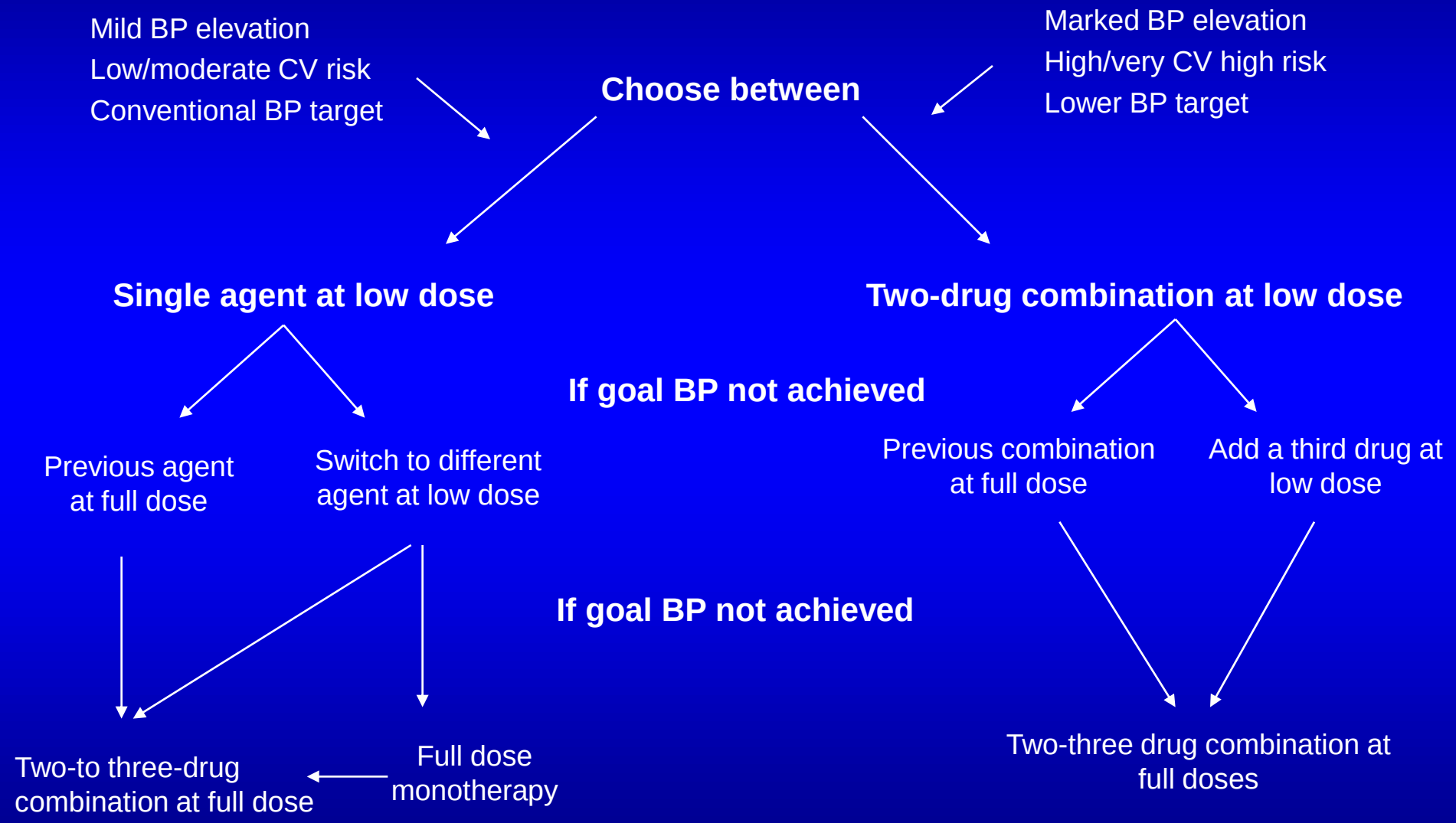
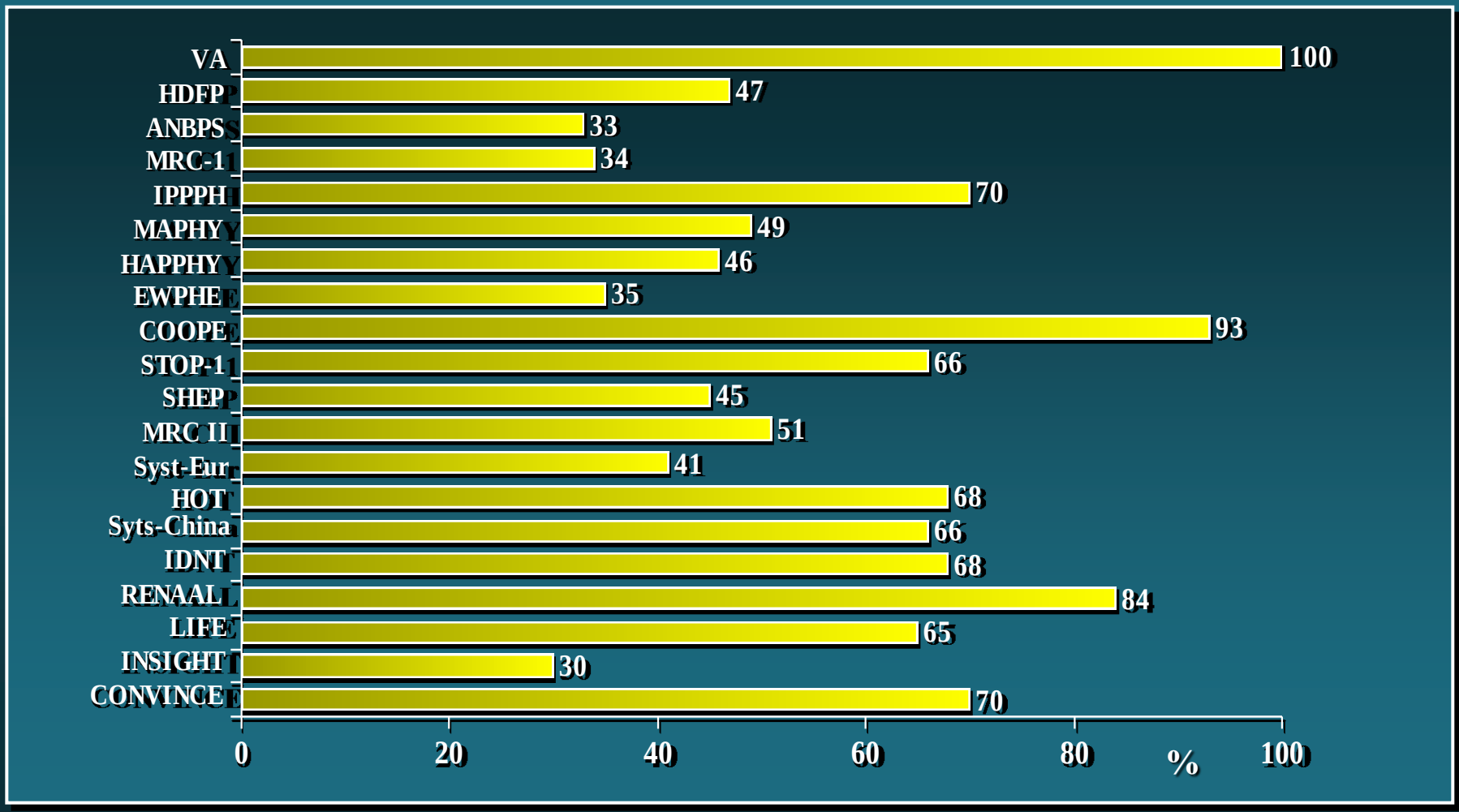
Monotherapy versus combination strategies



Percentage of Hypertensive Patients under Combination Treatment in Clinical Trials



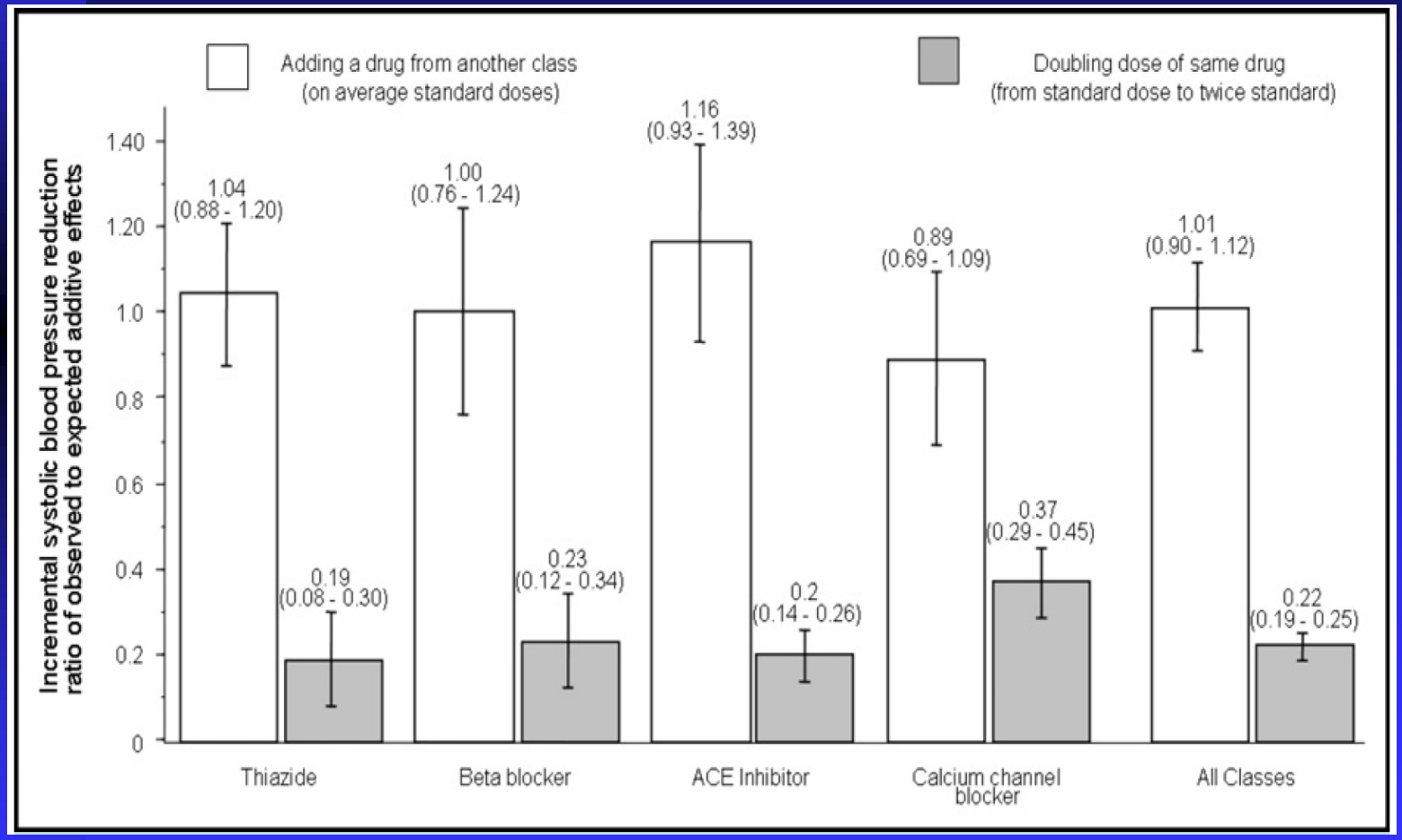
High percentage of combination treatment in recent clinical studies

Trials	% patients receiving ≥ 2 drugs at the end of the study
LIFE	90 - 91%
ASCOT	86 - 91%
ACCOMPLISH *	100%
ADVANCE *	100%

*** first step using a fixed-dose combination.**

Combination of 2 antihypertensive agents is approx. 5x more effective for SBP decrease compared to double dose of monotherapy

meta-analysis of 42 studies in 10,969 hypertensives



Wald et al. Ann Int Med 2009

Antihypertensive Agents, Compliance

Compliance, Safety, and Effectiveness of Fixed-Dose Combinations of Antihypertensive Agents

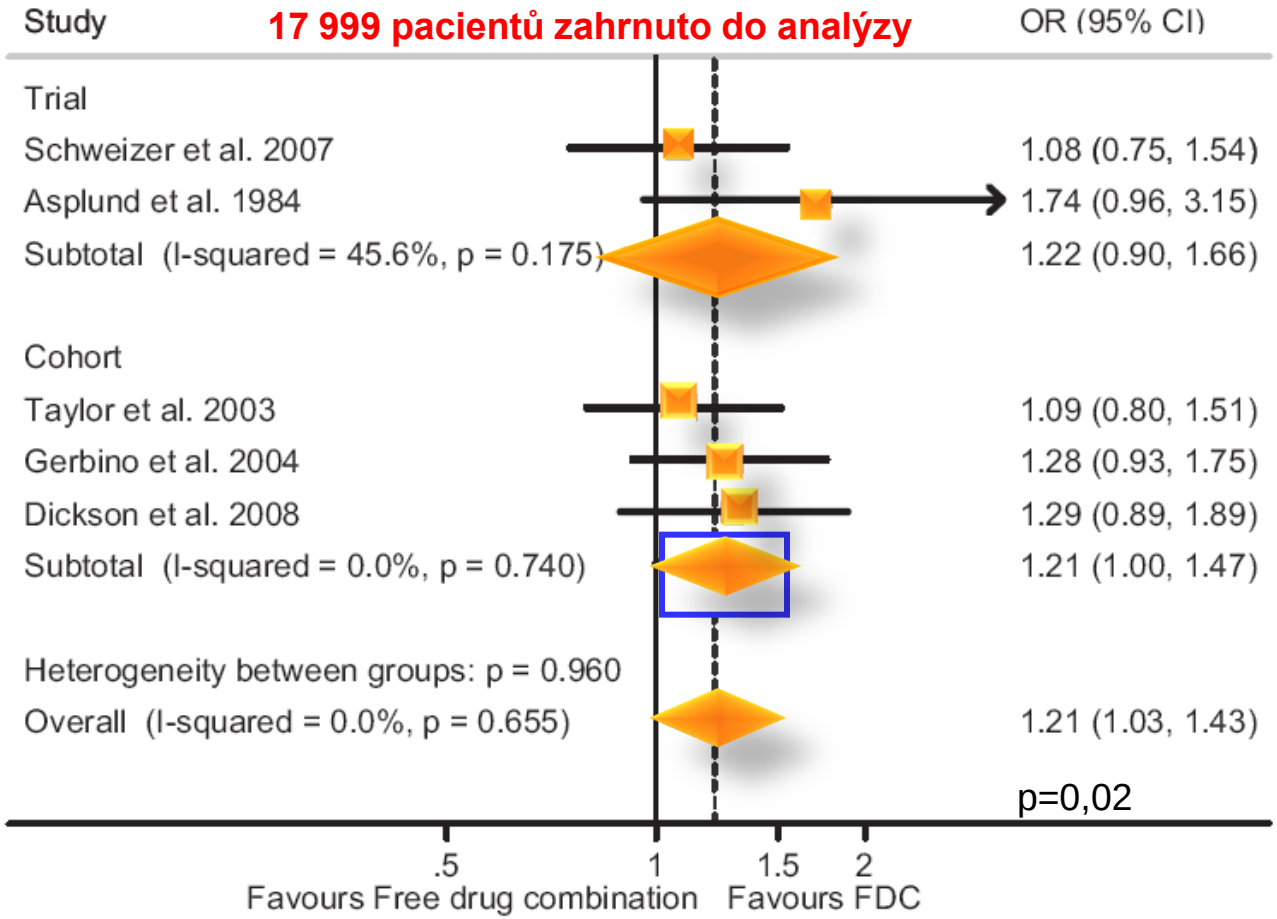
A Meta-Analysis

Ajay K. Gupta, Shazia Arshad, Neil R. Poulter

Hypertension 2010;55:399-407

Fixed combination and adherence

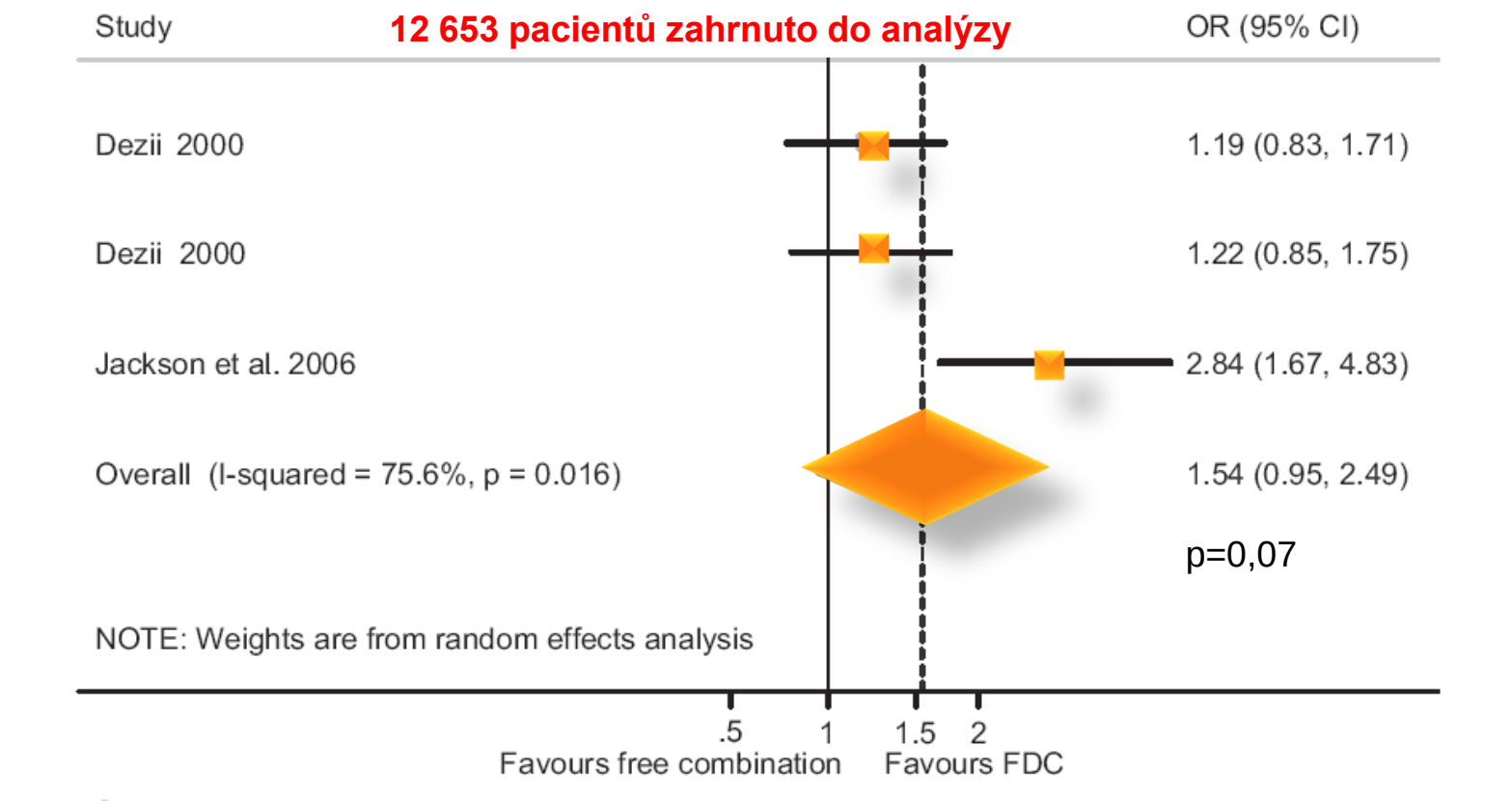
FIXED COMBINATION INCREASE TH E ADHERENCE TO THERAPY BY 21% COMPARED TO FREE COMBINATIONS



Gupta AK., et al. Hypertension 2010;55:399-407

FIXED COMBINATIONS AND PERSISTANCE

FIXED COMBINATIONS INCREASE LONG TERM PERSISTANCE BY 54%



Gupta AK., et al. Hypertension 2010;55:399-407

Combination of two antihypertensive agents and clinical evidence

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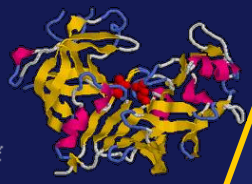
Discovery of RAS blockers

1898

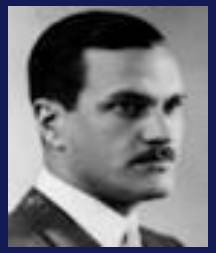
Tigerstedt & Bergman
Objev reninu a vlivu na ↗TK
(Scand Arch Physiol 1898: Niere und Kreislauf)

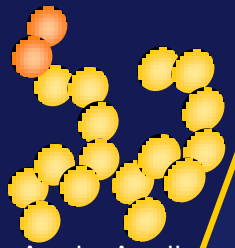


renin

1940

Braun-Menendez & Page
Objev hypertensinu (angiotenzinu)

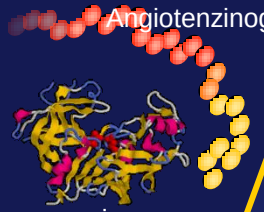




Ang I Ang II

1957

LT Skeggs
Objev 3 cest inhibice RAAS (renin, ACE, blokáda Ang II)



Angiotenzinogen

renin

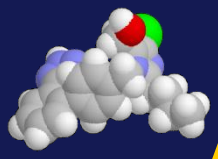
1967-1977

Cushman & Ondetti
Objev Captoprilu - ACEi

kaptopril

1986

Timmermans & Wong
Objev Losartanu – AT1B (Merck/Takeda)

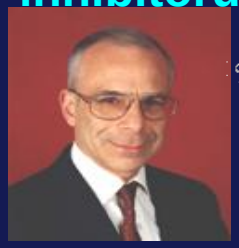


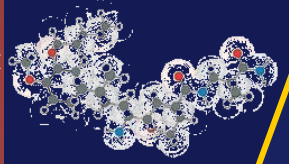
Losartan

losartan

2000

Novartis & Speedel
Výroba aliskirenu, 1. inhibitoru reninu

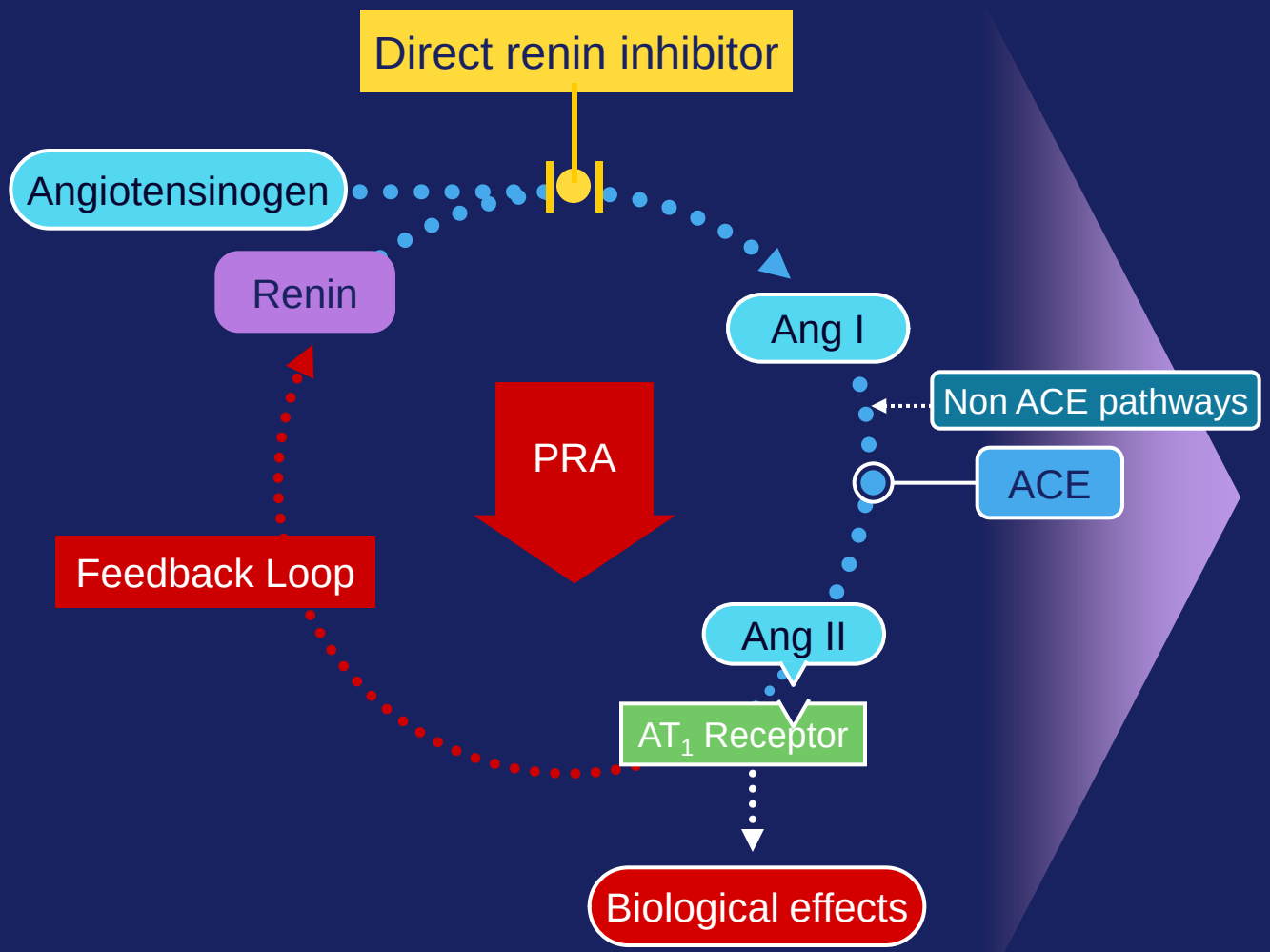




aliskiren

Adapted from: Müller DN & Luft FC. 2006. Ref.1.

Direct renin inhibitions block RAS and neutralize the increase of PRA



Ledviny
- Glomerulární vasokonstrikce
- Zánět
- Fibroza

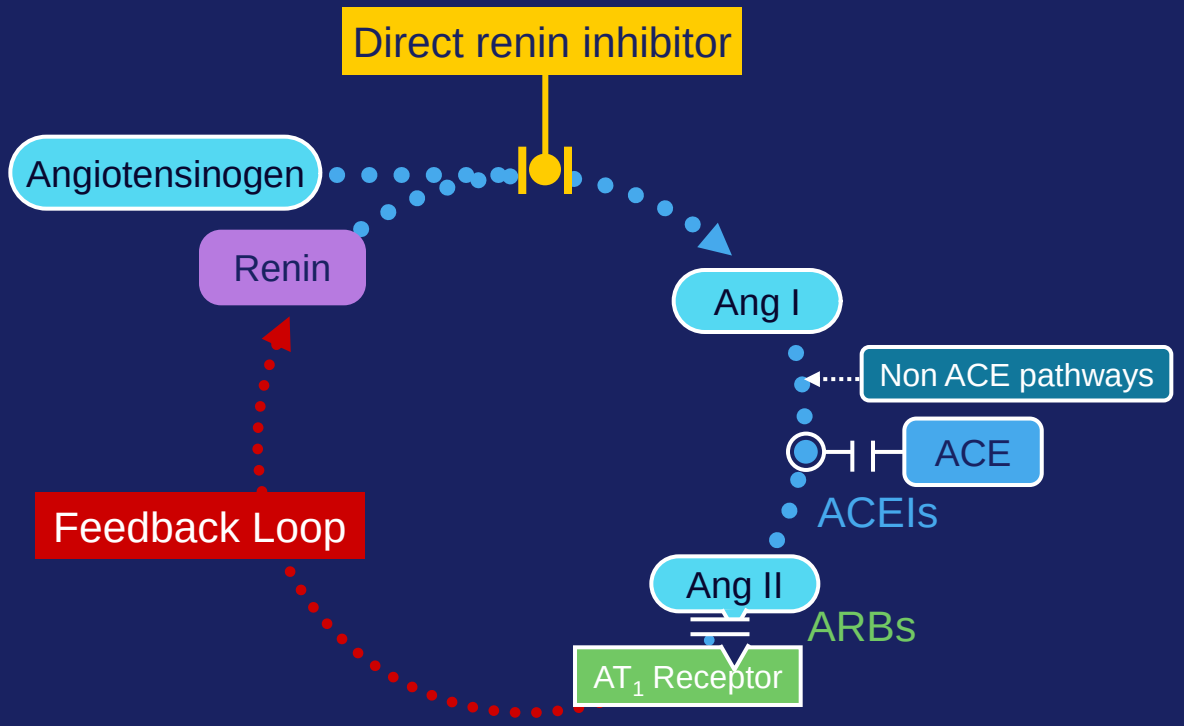
Srdce
- Hypertrofie
- Fibroza
- Vazokonstrikce

Cévy
- Hyperplázie, hypertrofie
- Zánět
- Oxidace
- Fibroza

Mozek
- Vazokonstrikce

Adapted from: Müller DN & Luft FC. 2006

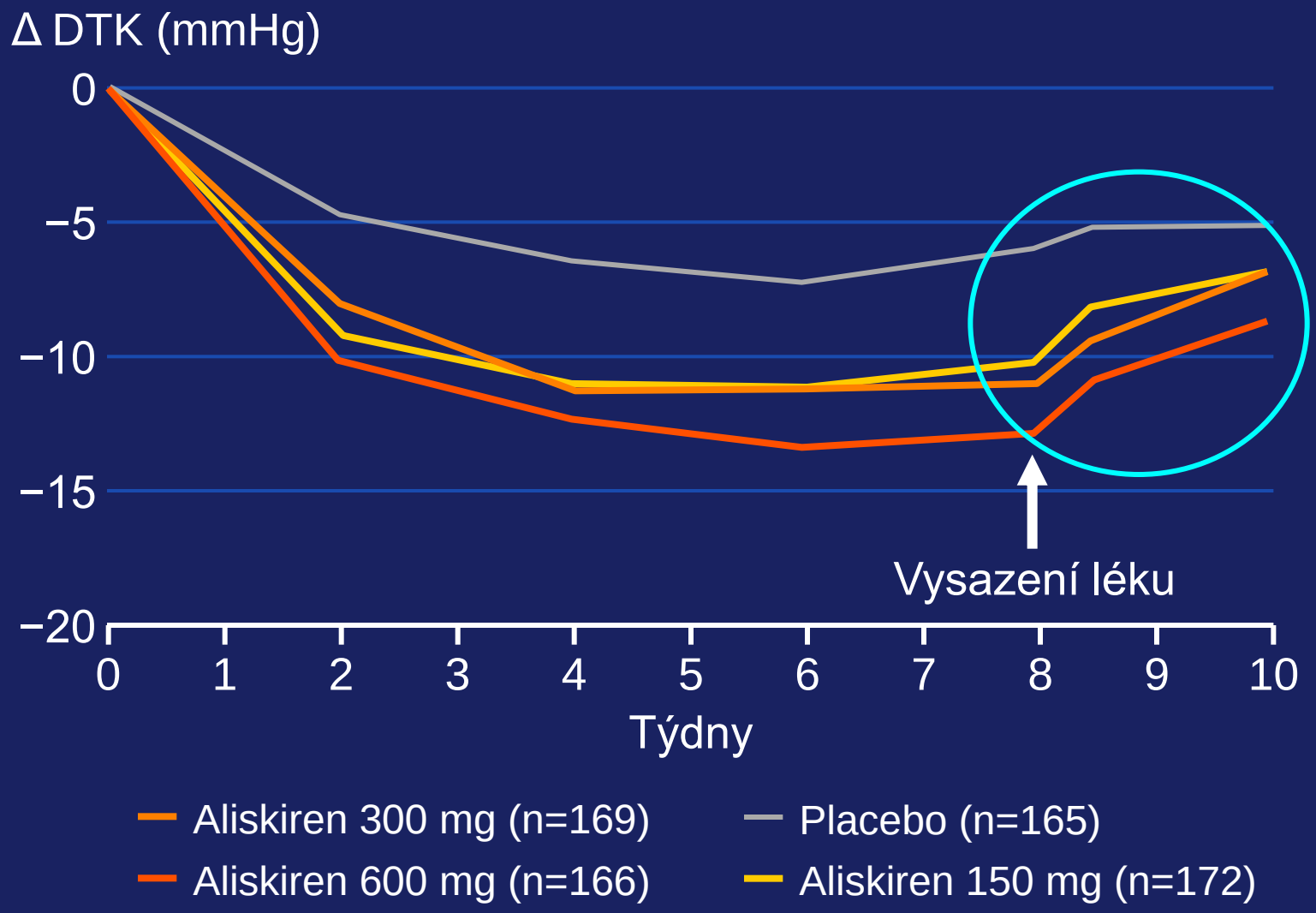
Effects of different RAS blockers on the components of RAS



	Ang I	Ang II	Renin	PRA
ACEI	↑	↓	↑	↑
AT1 blokátory	↑	↑	↑	↑
Aliskiren	↓	↓	↑	↓

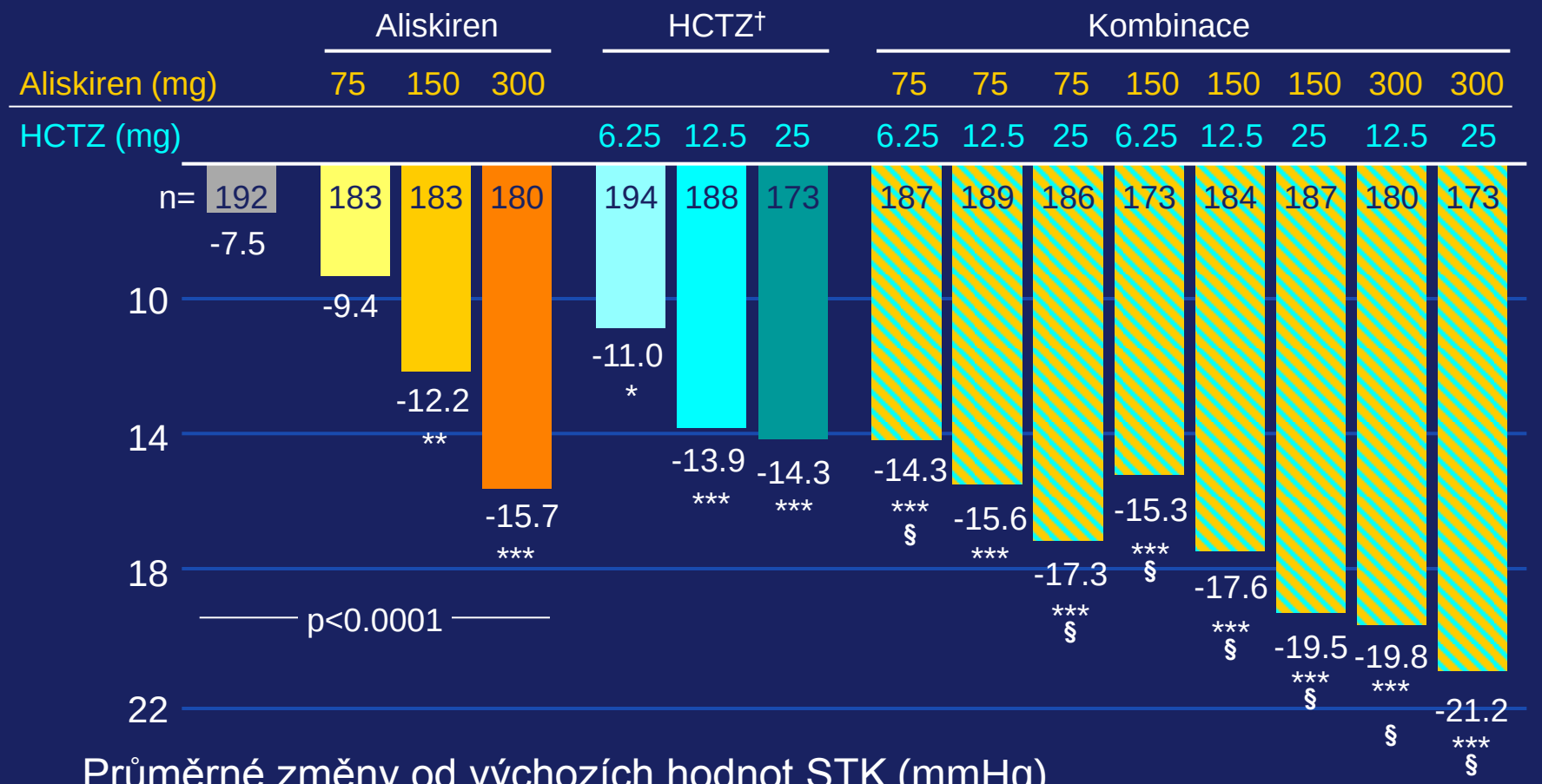
Azizi M & Ménard J. 2004

Antihypertensive effect of renin inhibitors after the withdrawal



Herron J, *et al*. 2006 (Study 2308)

Antihypertensive effects of aliskirenu, HCHT and combination



Průměrné změny od výchozích hodnot STK (mmHg)

†Celková významnost účinku HCTZ nebyla testována
Vzájemné srovnání:*p<0.05; **p<0.001; ***p<0.0001 vs. placebo;
§ p<0.05 vs. každá monoterapie

Villamil A, *et al*. 2006 (Study 2204)

Conclusions

- **BP variability – important risk and prognostic factor of CV disease/complications? ,**
- **Different effect of antihypertensive drugs/classes on BP variability?**
- **Target SBP values 130-139 mmHg in all hypertensives?**
- **Novel nonpharmacological approaches in resistant hypertension**
- **Combination treatment/fixed combination in most –approx. 80% of all patients?**
- **Renin inhibitors-new class of antihypertensive drugs**

Thank you for your attention

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