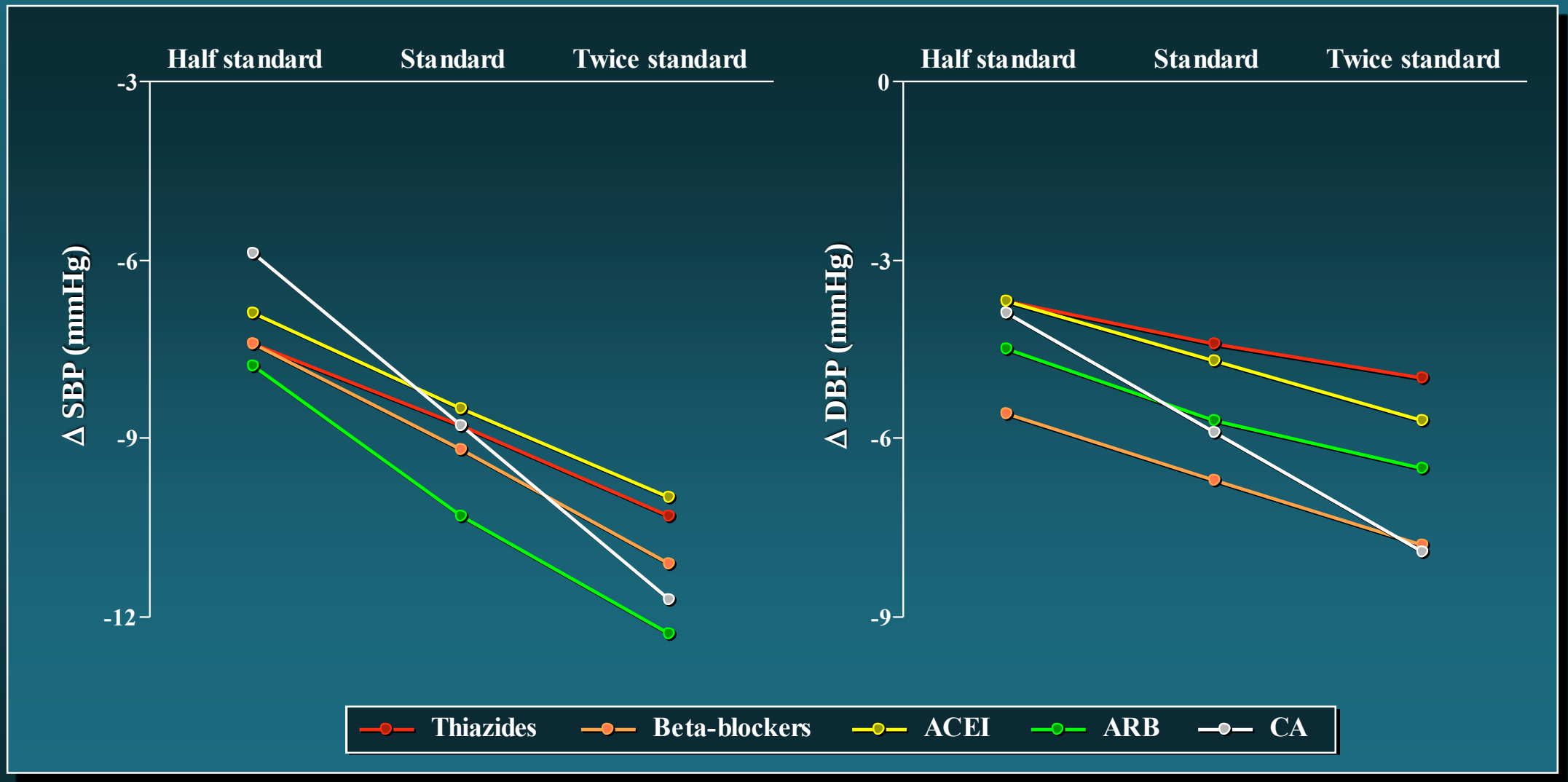
Drugs for the treatment of hypertension

- In previous Guidelines 5 major drug classes (ACEIs/ARBs/BBs/CCBs/Ds) were recommended based on
  - Proven ability to reduce BP
  - CV event reduction in placebo-controlled studies
  - Broad equivalence on overall CV morbidity/mortality
- These Guidelines recommend that the same 5 major classes of drugs should form the basis of antihypertensive therapy

Average BP ↓ over 24 Hours (Peak and Trough) from 357 Randomized Trials (n = 40000 Treated and 16000 Placebo Patients)

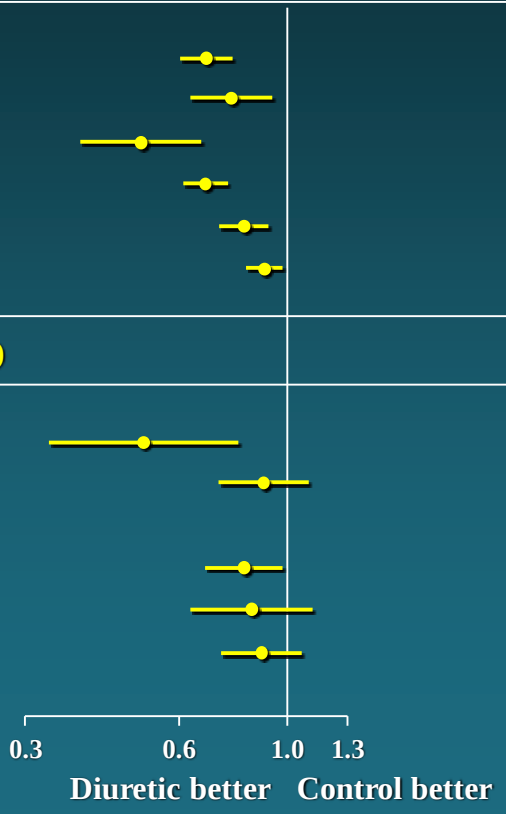


12437 M

Law MR et al., Brit Med J 2003; 326: 1427

Risk Reduction of Various Outcomes in Trials with Diuretics at Low/High Doses

Outcome	Trials (n)	Outcome risk (% in 5 years)	SBP/DBP Δ (mmHg)	RR (95% CI)	RR (95% CI)	Absolute Risk Reduction 1000 pts/5 years	NNT 5 years
Low doses (events = 7964)							
Stroke	8	9.9	-12.2/-5.1	0.68 (0.60-0.77)		-28	35
CHD	8	3.4	-12.2/-5.1	0.76 (0.63-0.92)		- 8	127
HF	5	4.7	-14.3/-5.0	0.51 (0.38-0.67)		-21	48
Stroke + CHD + HF	6	16.0	-14.4/-5.5	0.67 (0.61-0.75)		-51	20
CV Death	8	8.8	-12.2/-5.1	0.81 (0.72-0.91)		-16	63
All-cause Death	8	15.2	-12.2/-5.1	0.89 (0.82-0.97)		-16	61
High doses * (events = 6094)							
Stroke	3	1.9	-11.5/-5.7	0.51 (0.33-0.79)		-9	110
CHD	4	5.0	-10.4/-5.7	0.89 (0.73-1.09)		-5	184
HF	1						
Stroke + CHD + HF	2	4.0	-12.8/-5.5	0.81 (0.68-0.96)		-8	131
CV Death	4	2.4	-10.4/-5.7	0.84 (0.64-1.11)		-4	257
All-cause Death	4	4.3	-10.4/-5.7	0.88 (0.74-1.06)		-5	192

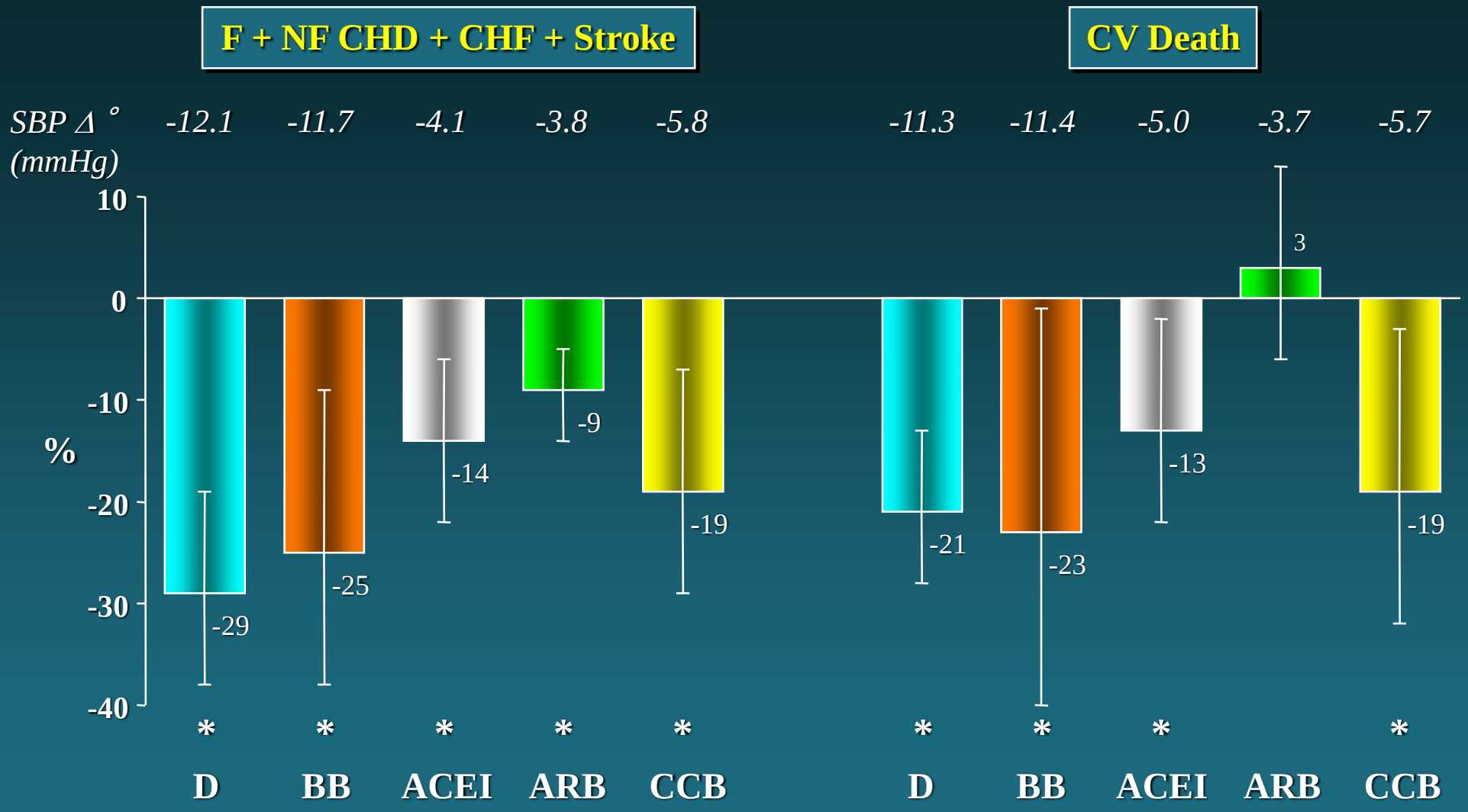


* Chlorth. or HCTZ ≥ 50 mg / Indapamide or bendrofluazide ≥ 5 mg

19525 M

Thomopoulos et al., J Hypertens 2015; 33; 195

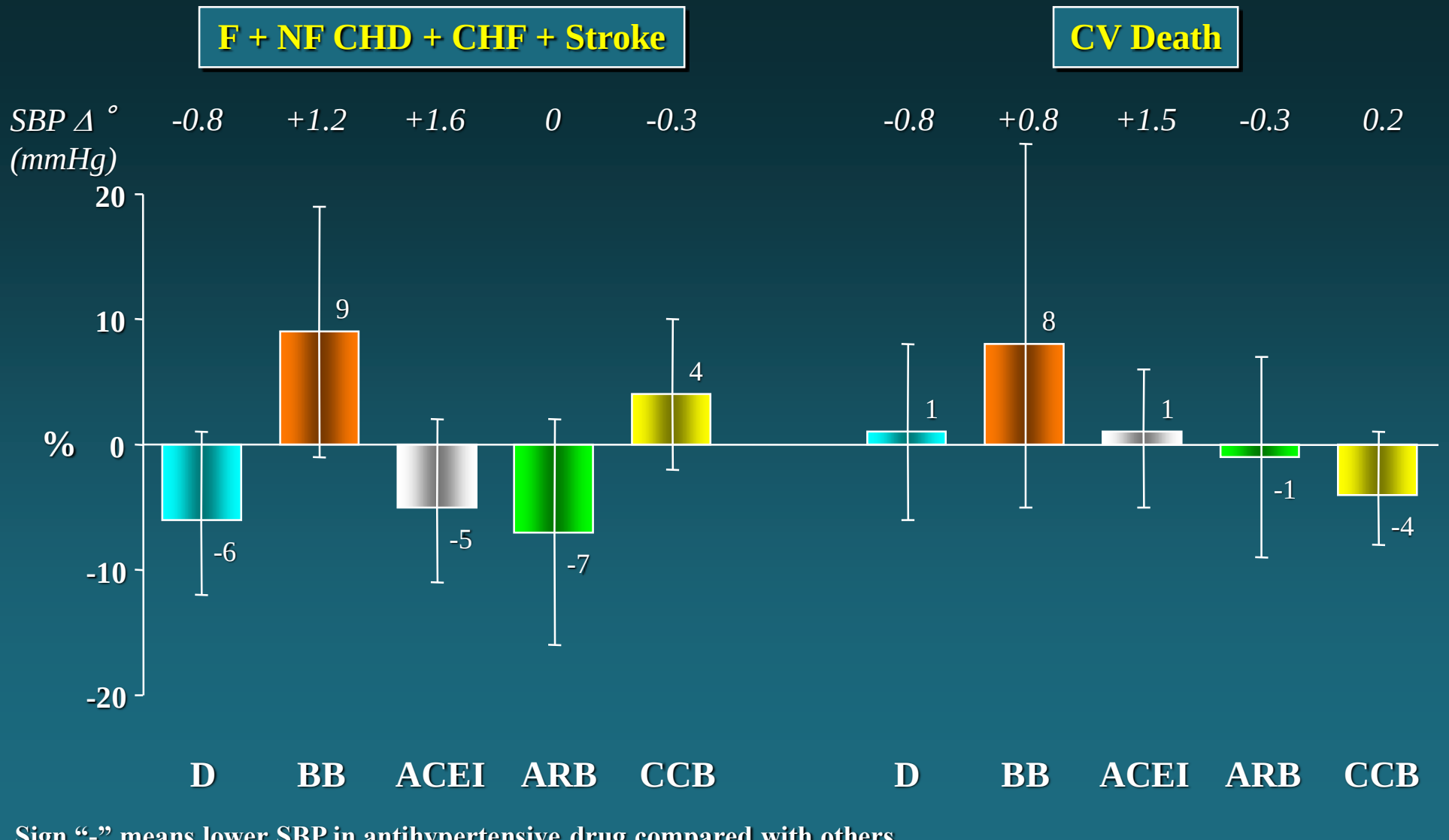
Risk of CV Morbidity and Mortality in RCTs Comparing Drug Treatment vs Placebo



° Sign "-" means lower SBP in drug group; * Statistically significant

Thomopoulos et al., J Hypertens 2015; 33: 132

Risk of CV Morbidity and Mortality in RCTs
Comparing One Antihypertensive Drugs Class vs Others



° Sign "-" means lower SBP in antihypertensive drug compared with others

Thomopoulos et al., J Hypertens 2015; 33: 132

Risk of cause-specific outcomes with Diuretics vs all other agents

	Stroke	Heart Failure	CHD
Law (2009)	-6 (NS)	-9%(NS)	-1%(NS)
Thomopoulos (2015)	-4%(NS)	-17%*	+3%(NS)
Ettehad (2015)	-3%(NS)	-19%*	+2%(NS)

* Statistically significant

Hypertension drug treatment strategies

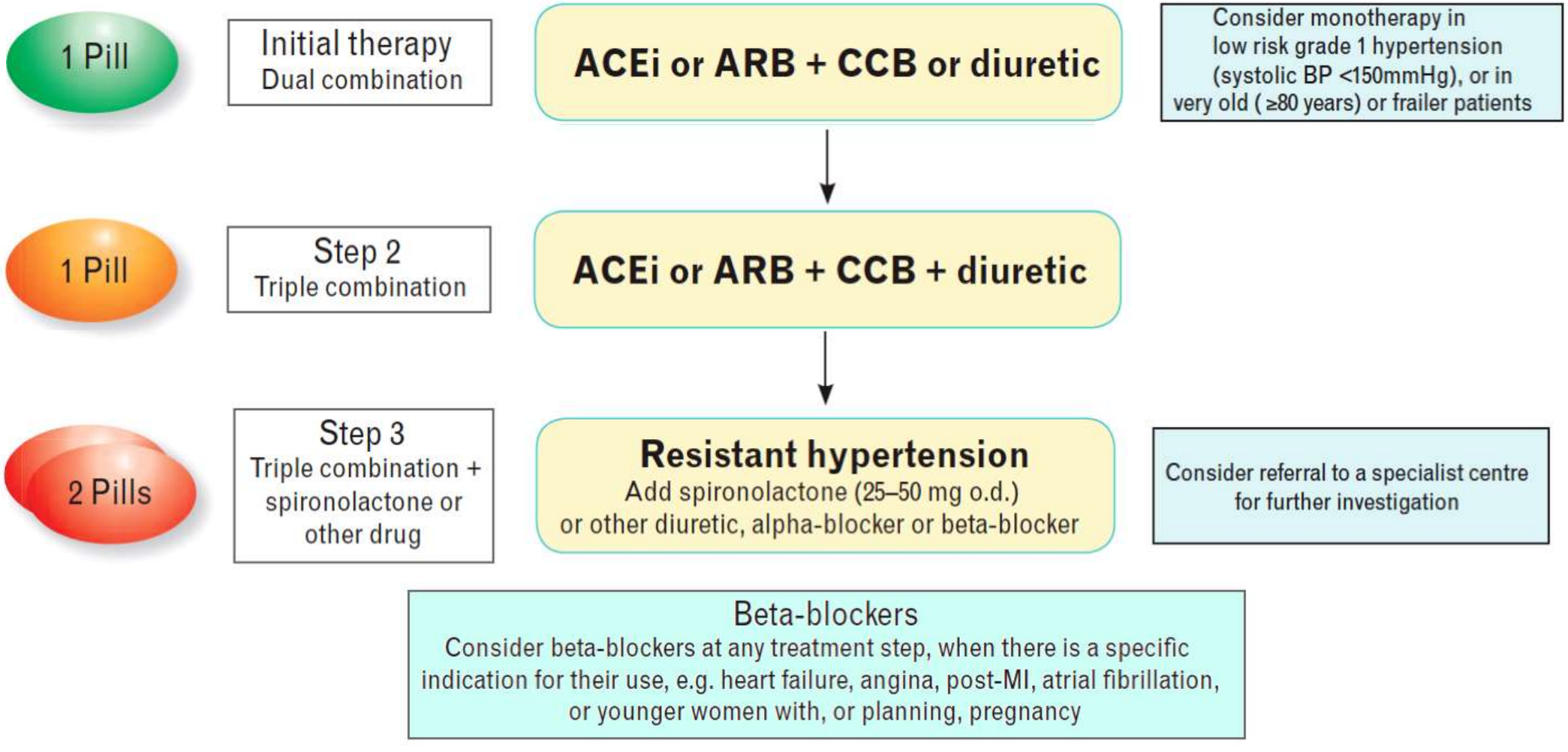
- Increasing dose of initial monotherapy (side effects/ineffective)
- Substitution with another monotherapy (time consuming/ineffective)
- Stepped-case approach,i.e.monotherapy with sequential addition of other drugs in most pts (monotherapy remains predominant)
- Two major barriers:LOW ADHERENCE/THRAPEUTIC INERTIA

Rationale for initial two-drug combination therapy in most patients

- Greater BP reduction vs monotherapy
- Reduced heterogeneity of the BP response
- Steeper dose- BP response relationship
- No /Small increase in hypotensive episodes
- Better adherence to treatment
- Reduced therapeutic inertia
- Better long-term BP control
- Reduced CV events vs initial monotherapy in observational studies

Williams, Mancia et al., J Hypertens 2018 and Eur Heart J 2018, in press

Core drug-treatment strategy for uncomplicated hypertension



The core algorithm is also appropriate for most patients with HMOD, cerebrovascular disease, diabetes, or PAD

Williams, Mancia et al., J Hypertens 2018;36:1953-2041 and Eur Heart J 2018;39:3021-3104

Major drug combinations used in trials in a step-wise or randomized approach vs placebo,monotherapy or other combinations

ACEI + D

- CAPPP
- ADVANCE
- PROGRESS
- HYVET
- ACCOMPLISH

ACEI + CCB

- ACCOMPLISH
- NORDIL
- INVEST
- ASCOT
- Syst-Eur
- Syst-China

ARB + D

- LIFE
- SCOPE
- COLM

CCB + D

- ELSA
- CONVINCE
- VALUE
- COPE
- FEVER

BB + D

- COPE
- SHEP
- STOP-2
- CONVINCE
- CAPPP
- STOP-I
- LIFE
- NORDIL
- Coope & Warrender
- INVEST
- ALLHAT
- ASCOT

ACEI + ARB (or renin inhibitor)

- ONTARGET
- ALTITUDE

ACEI + BB

- ALLHAT

CCB + BB

- ALLHAT
- COPE

ARB + CCB

- COPE
- COLM

Reduction of the Risk of Stroke with Different Diuretics at Low Doses

	All events	Δ SBP (mmHg)	RR	RR (95% CI)
Thiazides	3006	-17.3		0.59 (0.41-0.85)
Chlorthalidone	2219	-13.4		0.63 (0.50-0.80)
Indapamide	2269	- 8.5		0.73 (0.61-0.87)

19770 M

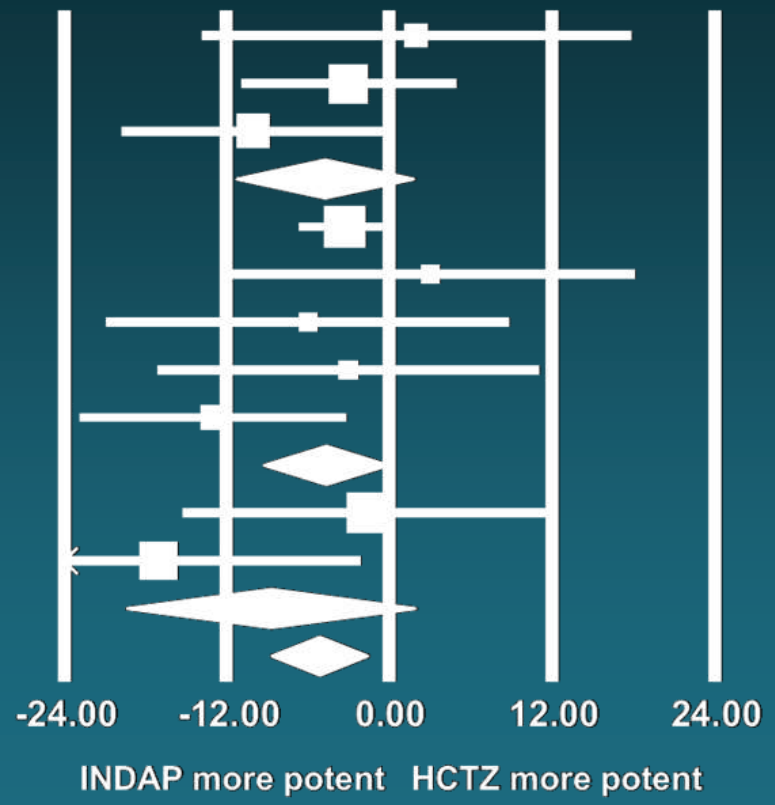
Thomopoulos et al., J Hypertens 2015; 33: 195

Which diuretic/Considerations of 2018 ESC/ESH GLs

- Thiazides/Chlortalidone/Indapamide have all been used in outcome-based RCTs with positive results
- Superiority of one diuretic type over another never tested in head-to-head trials
- In absence of evidence from comparative trials (and recognizing that many SPCs are based on HCTZ) all three diuretics can be considered suitable antihypertensive agents

For systolic blood pressure, random effects, DerSimonian–Laired metaanalysis comparing HCTZ and indapamide

Group by Dose Level	Study name	Statistics for each study: Difference in means	Lower limit	Upper limit	p-Value
Dose Equivalent	Elliott	2.000	-13.680	17.680	0.803
Dose Equivalent	Malini	-3.000	-10.785	4.785	0.450
Dose Equivalent	Spence	-10.050	-19.642	-0.458	0.040
Dose Equivalent		-4.744	-11.254	1.767	0.153
HCTZ Higher	Emeriau	-3.300	-6.542	-0.058	0.046
HCTZ Higher	Kreeft	3.000	-11.987	17.987	0.695
HCTZ Higher	Madkour	-6.000	-20.743	8.743	0.425
HCTZ Higher	Plante a	-3.000	-16.960	10.960	0.674
HCTZ Higher	Plante b	-13.000	-22.705	-3.295	0.009
HCTZ Higher		-4.657	-9.225	-0.089	0.046
INDAP Higher	Krum	-1.600	-15.146	11.946	0.817
INDAP Higher	Radevski	-17.000	-31.761	-2.239	0.024
INDAP Higher		-8.717	-19.345	1.910	0.108
Overall		-5.130	-8.657	-1.602	0.004



HCTZ: hydrochlorothiazide; INDAP: indapamide

20596 M

Roush GC et al., Hypertension. 2015;65:00-00. DOI: 10.1161/HYPERTENSIONAHA.114.05021.)

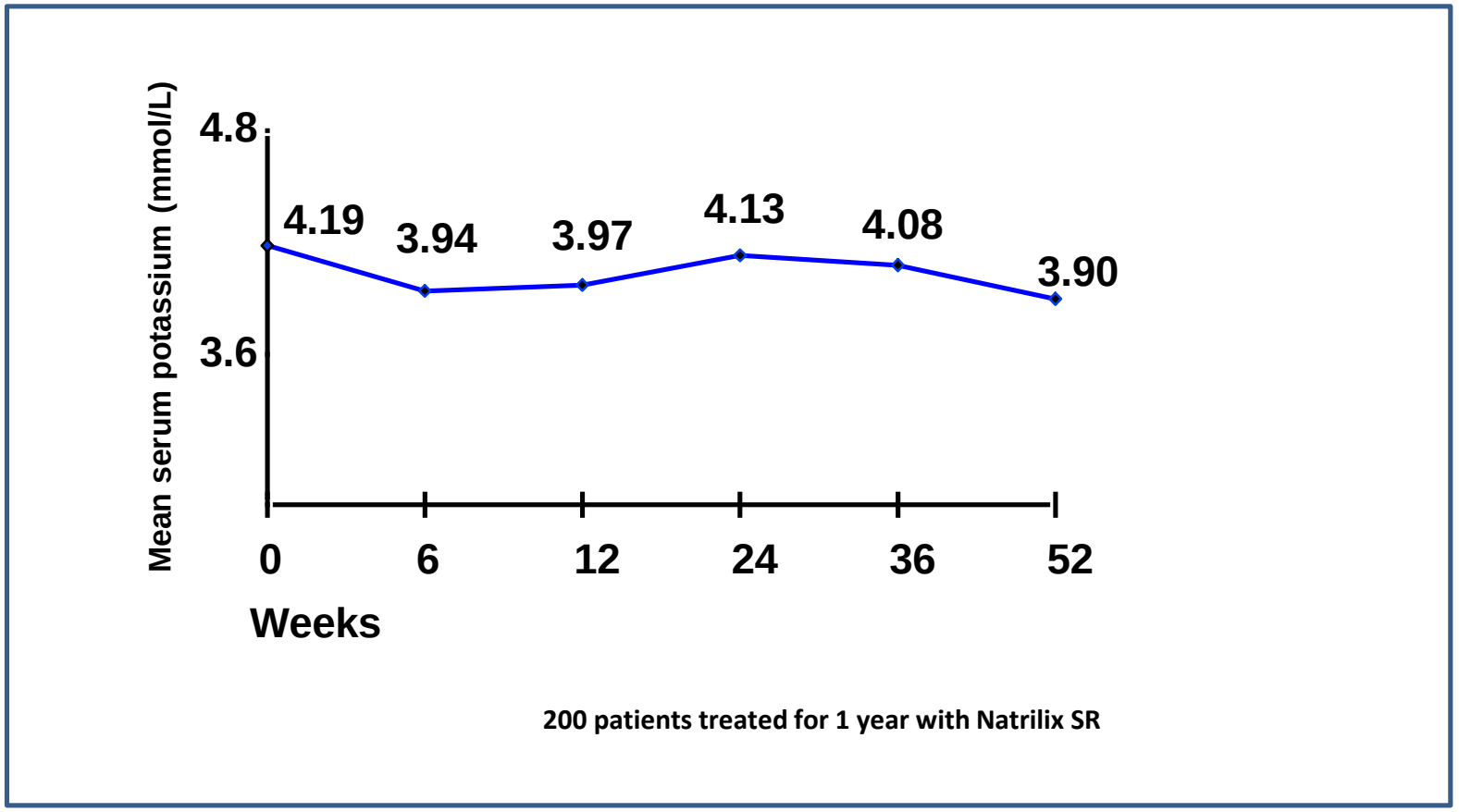
Trends for adverse metabolic effects from HCTZ compared with indapamide with change

Adverse Effect	Change from INDAP minus change from HCTZ (95% CI)	Units
Low potassium	−0.1 (−0.3 to 0.2)	mEq/L
Low sodium	1 (−1 to 3)	mEq/L
High creatinine	0.1 (−0.1 to 0.2)	mg/dL
High glucose	4 (−3 to 11)	mg/dL
High cholesterol	−5 (−17 to 7)	mg/dL
High uric acid	−0.2 (−0.7 to 0.4)	mg/dL

HCTZ: hydrochlorothiazide; INDAP: indapamide

Roush GC et al., Hypertension. 2015;65:00-00. DOI: 10.1161/HYPERTENSIONAHA.114.05021.)

No evidence of electrolyte imbalance

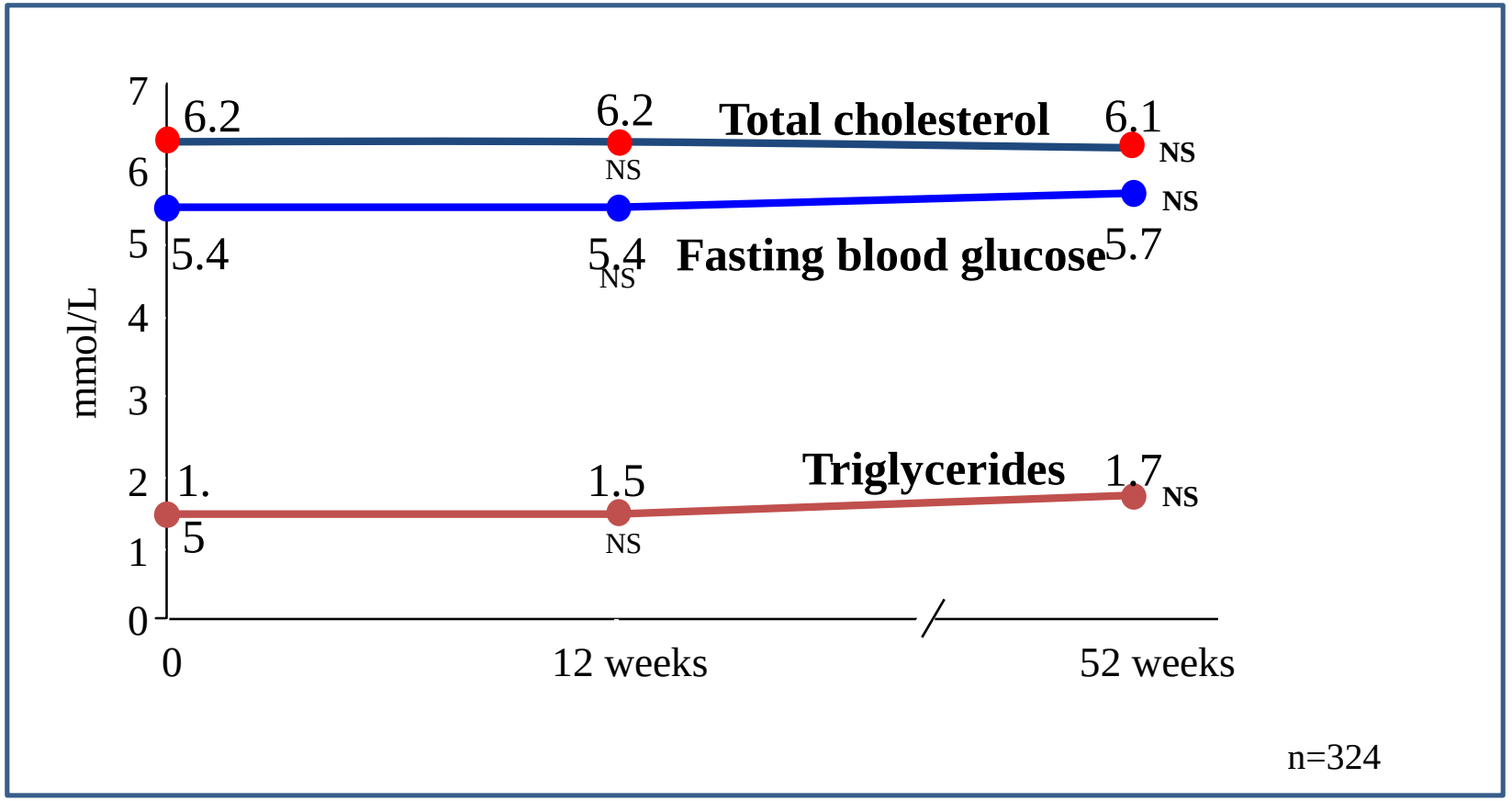


- Minimal incidence of hypokalemia
- No known reports of hyponatremia

Guez D. Arch Mal Coeur 1996;Special : 2-8

Indapamide SR

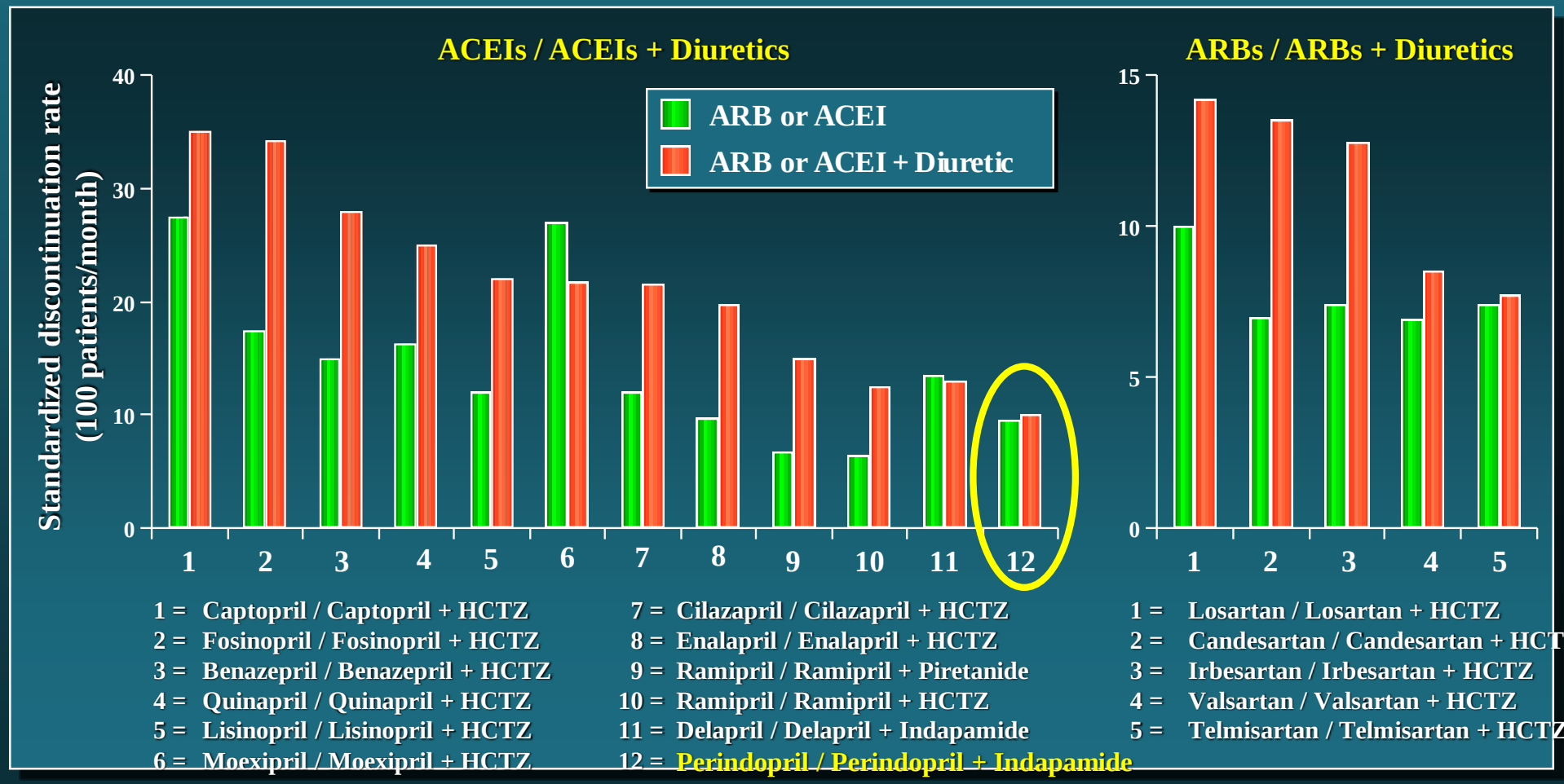
Complete metabolic safety



- **Lipid and glucose neutral over the long term**
- **Does not affect body weight and serum creatinine levels**

Ambrosioni E, Safar M, Degaute JP, et al. *J Hypertens*. 1998;16:1677-1684.

Increase in Discontinuation Rate with the Addition of a Diuretic to RAS Blockers



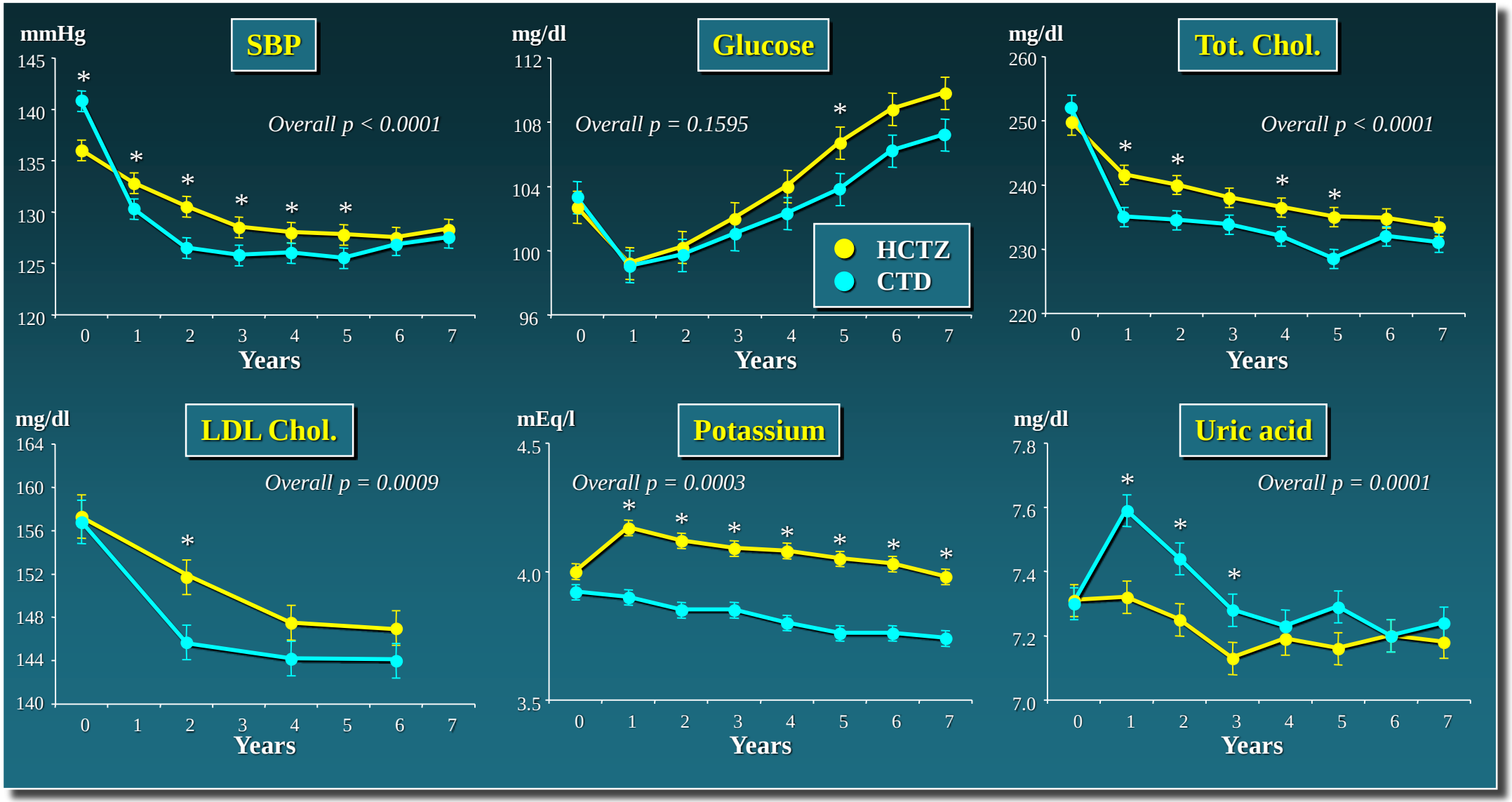
15140 M

Mancia,et al J Hypert 2011,29,1012-1018

Diuretic treatment in 2018 ESC/ESH GLs

- Lower dose thiazide-like diuretics have more evidence from RCTs demonstrating CV event reduction than lower dose HCTZ
- CHLORTALIDONE and INDAPAMIDE are more potent than HCTZ in lowering BP, with a longer duration of action
- …… and no evidence of a greater incidence of side effects

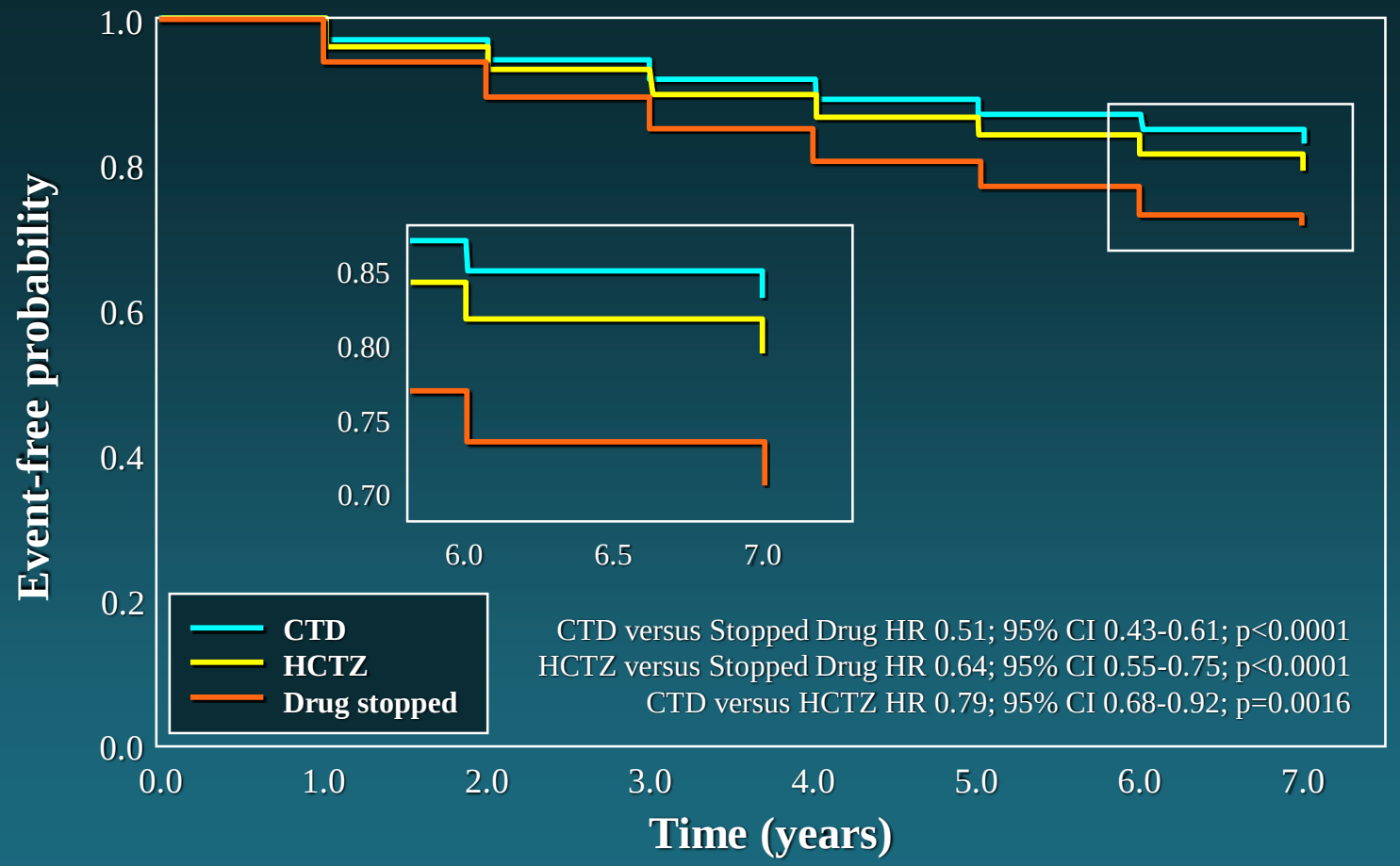
Effects of Chlorthalidone vs HCTZ over Time (Adjusted values)



Dorsch MP et al., Hypertension 2011; 57: 689

17173 M

Adjusted Event-free Probability of CVEs with Chlorthalidone or HCTZ



The hazard ratio was estimated using the Cox model. - Adjusted estimates were controlled for by age, race, smoking status, MRFIT randomized group, diuretic dose, SBP, LDL, HDL, and baseline hypertension treatment.

Dorsch MP et al., Hypertension 2011; 57: 689

Meta-analysis of comparison studies on Diuretics

- 21 studies (>480.000 patients)
- Compared to thiazides, thiazide-like diuretics reduced adjusted risk of

  -CV events by 12% (P= 0.049)

  -Heart Failure by 21% (P= 0.023)

Engberink et al, Hypertension 2015,65,1033

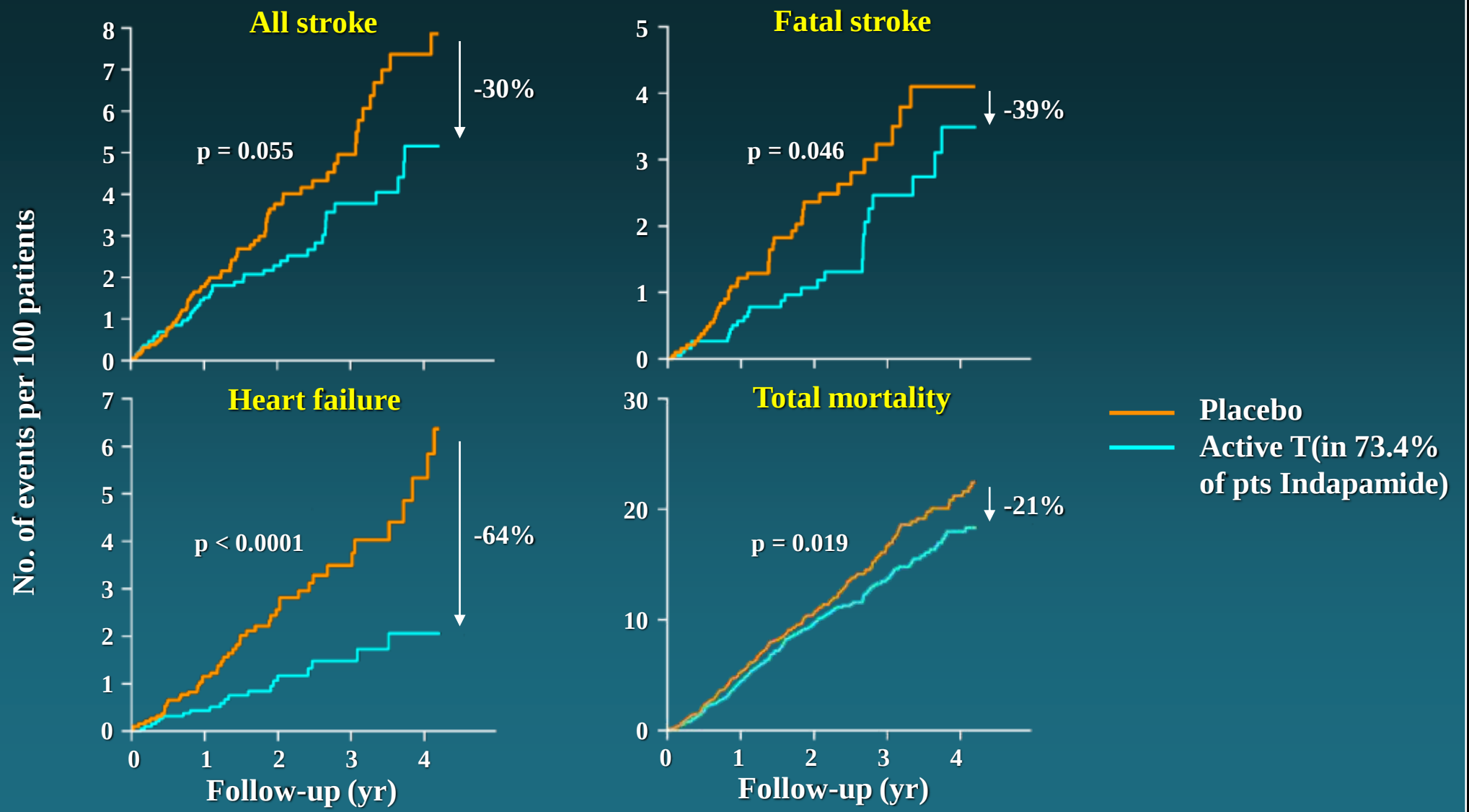
Evidence of CV benefits with Indapamide SR

Trial	Dose (mg)	Results
PATS[1]	2.5	Significant CV benefits vs placebo
HYVET[2]	1.5 SR (+/- perindopril)	Significant reduction in All Cause Mortality, Stroke & HF vs placebo
PROGRESS[3]	2.5 (+ perindopril)	Significant CV benefits vs placebo
ADVANCE[4] *(diabetic patients)*	1.25 (+ perindopril)	Significant reduction in All Cause Mortality & CV events vs placebo

Same dose is used clinically, with good metabolic safety

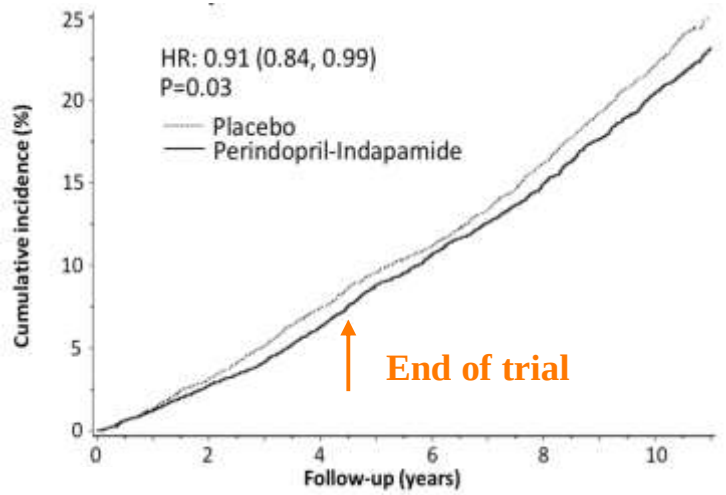
1. PATS, ***Chinese Med Jour*** **1995;108(9):710-717; 2. HYVET,** ***NEJM*** **2008;358:1887-1898; 3.** PROGRESS Collaborative Group, *Lancet.* 2001;358:1033-1041; 4.ADVANCE-BPLA Collaborative Group, *Lancet* 2007;370:829-840.

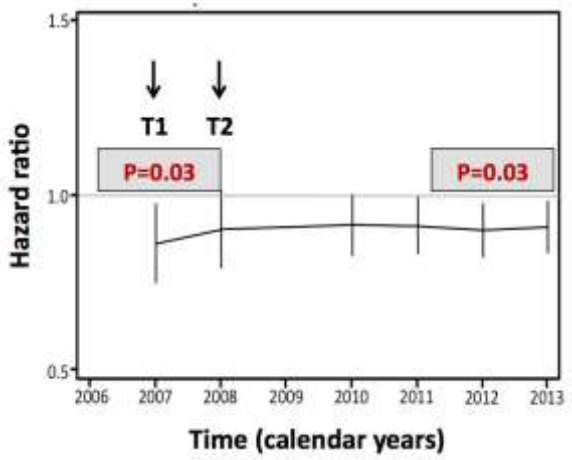
Incidence of Morbidity / Mortality in HYVET



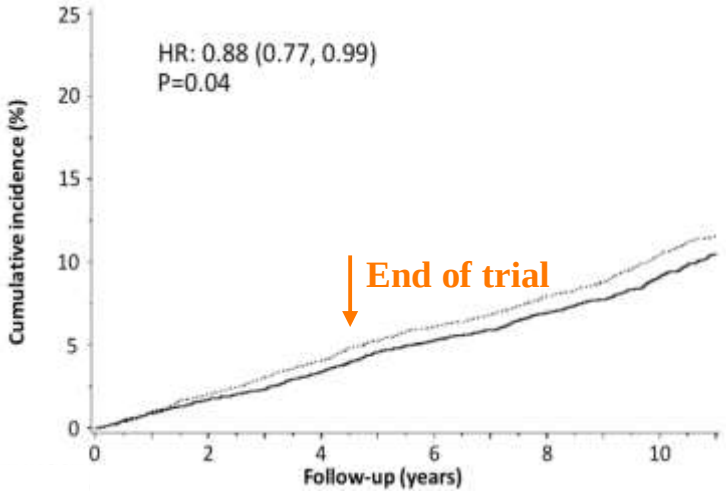
Mortality in ADVANCE-ON Study (overall follow-up 9.9 ys)

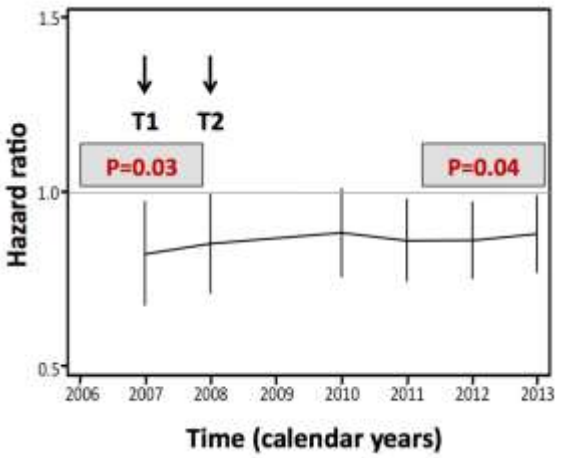
All-cause mortality





CV mortality





19183 M

Zoungas, Chalmers,Mancia et al NEJM, 2014, Sept 19

Head-to-Head Comparisons of Hydrochlorothiazide with Indapamide and Chlorthalidone

Antihypertensive and Metabolic Effects

Roush GC et al., Hypertension. 2015;65:00-00. DOI: 10.1161/HYPERTENSIONAHA.114.05021.)

Diuretic treatment in 2018 ESC/ESH GLs

- Lower dose thiazide diuretics have more evidence from RCTs demonstrating CV event reduction than lower dose HCTZ
- CHLORTALIDONE and INDAPAMIDE are more potent than HCTZ in lowering BP, with a longer duration of action and no evidence of a greater incidence of side effects

Diuretics (alone / combination) in the Treatment of Hypertension - Use in Event-based / Randomized Trials

- Chlorthalidone → 4 Trials
- HCTZ / Other thiazides* → 12 Trials
- Indapamide → 4 Trials

* Mainly HCTZ / sometimes not

Difference in SBP and Metabolic Effects between Indapamide - HCTZ

	Difference in means (Indapamide -HCTZ)
SBP reduction (mmHg)	+5.1 (+8.6 / +1.6)
K^+ reduction (mEq/l)	+0.054 (+0.3 / +0.19)
Glucose increase (mg/dl)	+4.0 (-3 / +11)
Cholesterol increase (mg/dl)	-5.0 (-17 / +7)
Uric acid increase (mg/dl)	-0.2 (-0.7 / 0.4)

Roush et al., Hypertension 2015; 65: 1041

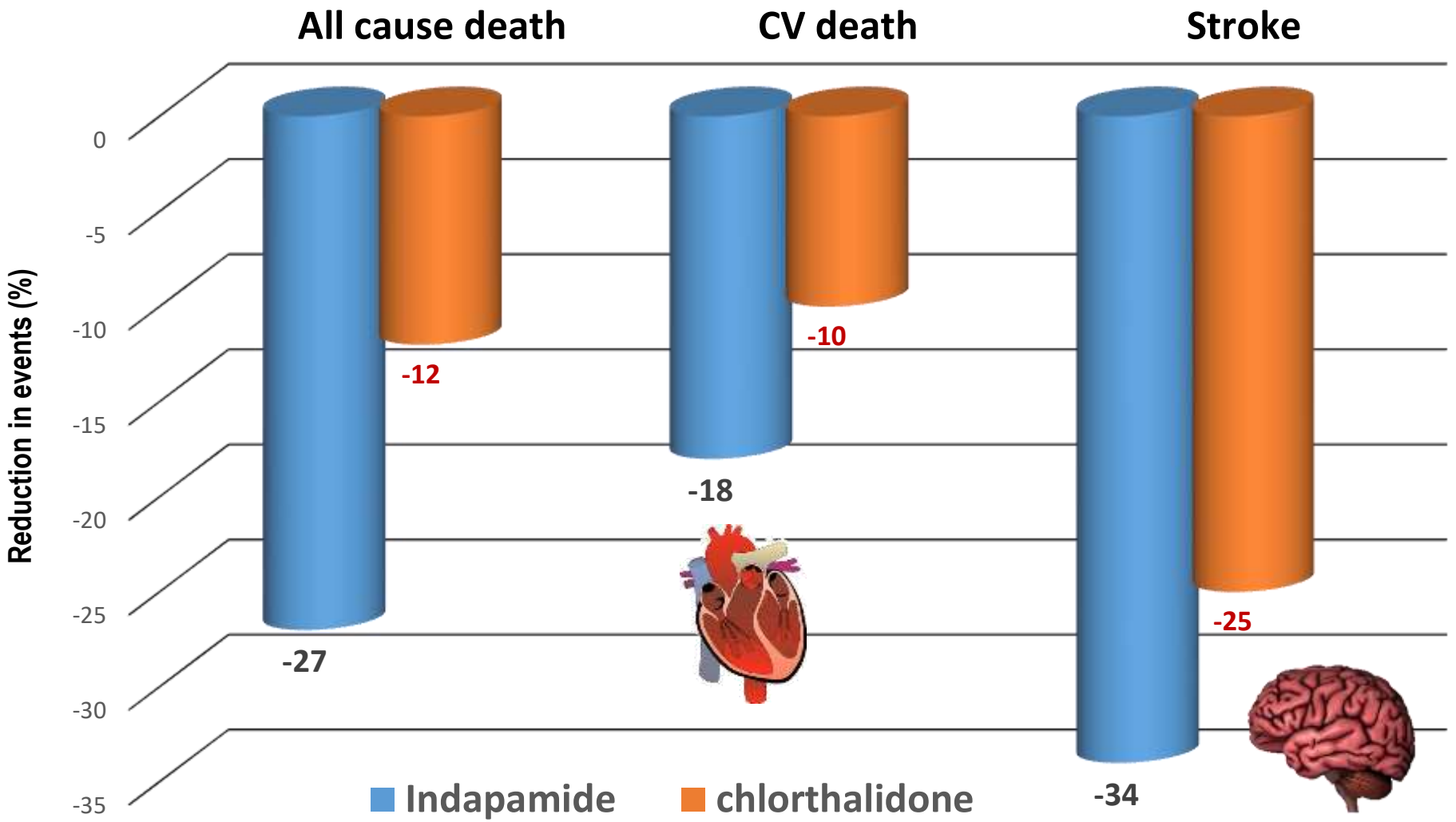
Risk of T discontinuation (vs placebo) in trials

- Diuretics 2.23 (1.32-3.76)
- Beta-blockers 2.88 (1.58-5.28)
- Calcium antagonists 2.03 (1.17-3.56)
- ACE inhibitors 2.78 (1.37-5.74)
- AT1 Receptor blockers 1.13 (0.78-1.62)

Thomopoulos et al, J Hypertens 2016,34,1921

Meta-analysis:
Indapamide SR superior to chlorthalidone

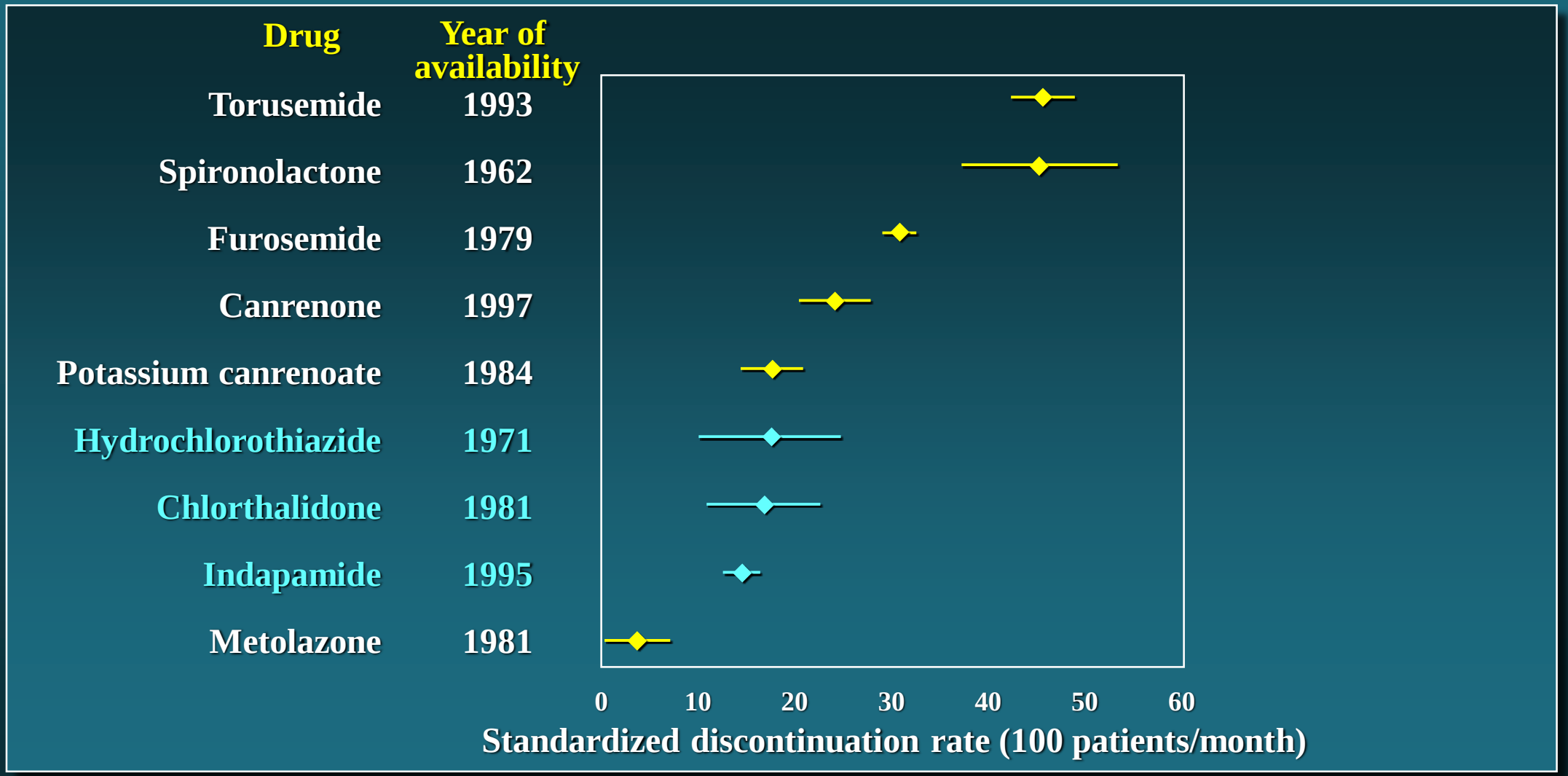
55 randomized trials; n=195,267 patients



Costas Thomopoulos et al , Journal of Hypertension 2015, 33.

Discontinuation of Initial Monotherapy within Antihypertensive Drug Class

Diuretics



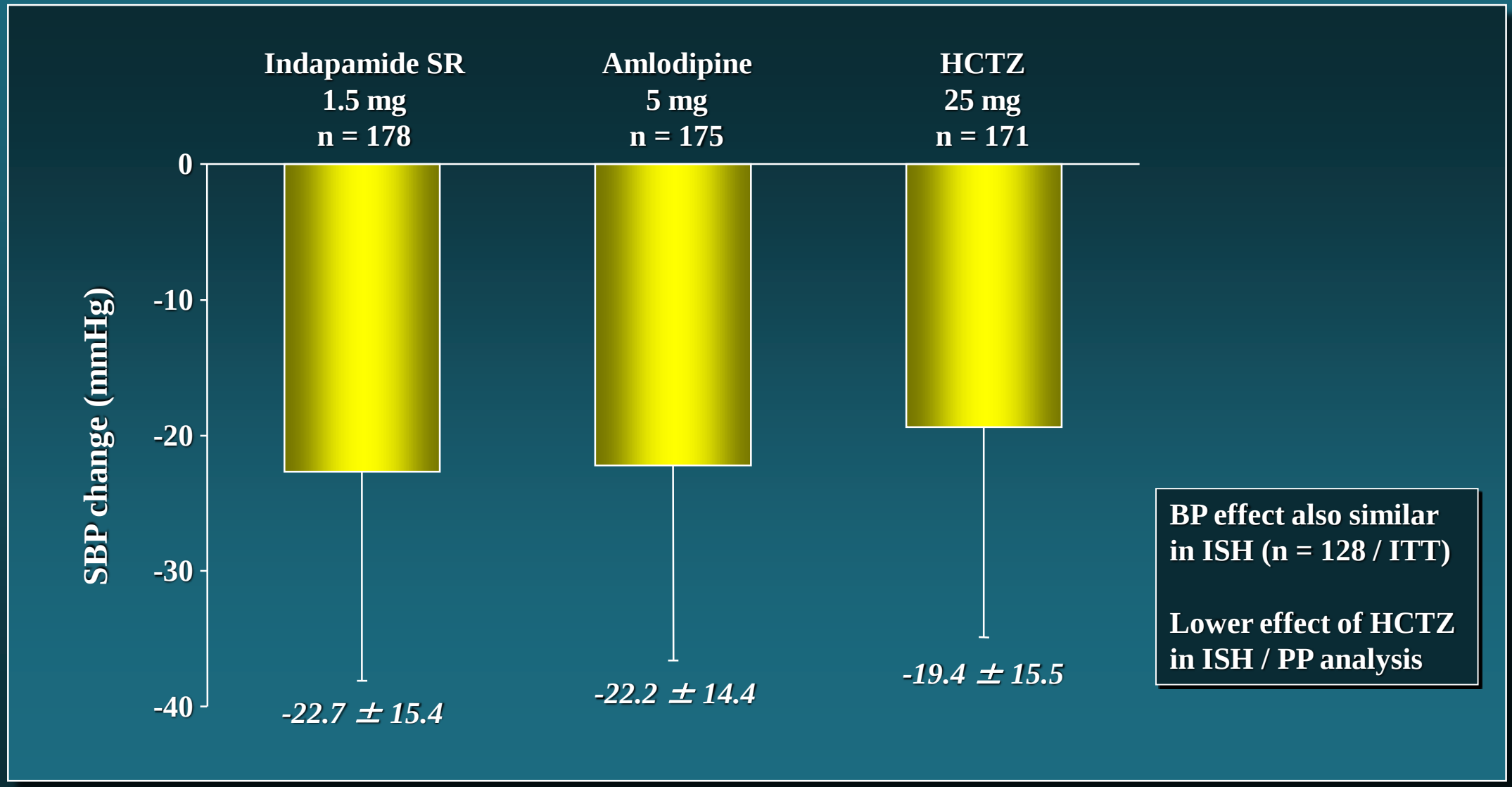
15144 M

Mancia et al., J Hypert 2011; 29: 1012-1018

Questions about diuretics

- All have RCT-based evidence of CV protection
- No event-based RCT comparison/Claim of event-based differences derived from post-hoc uncontrlled data
- Duration of action? BP-lowering effects?
- New onset diabetes/effects on serum potassium-glucose-lipids?
- Side effect profile?
- Mechanisms of action?

SBP Reduction in Elderly Hypertensives (R / DB study; ITT)

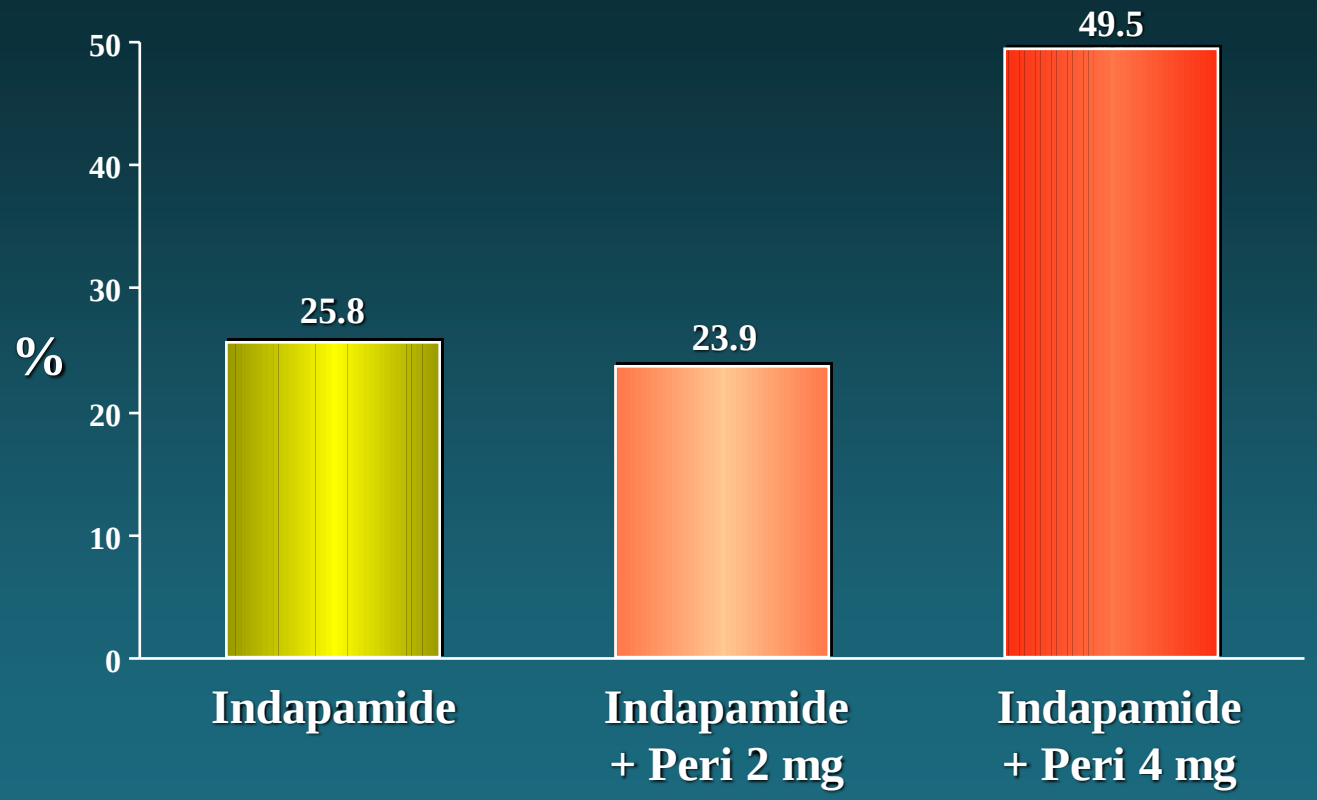


Emeriau et al., J Hypertens 2001; 19: 343

Fundamental principles in 2018 ESC/ESH GLs

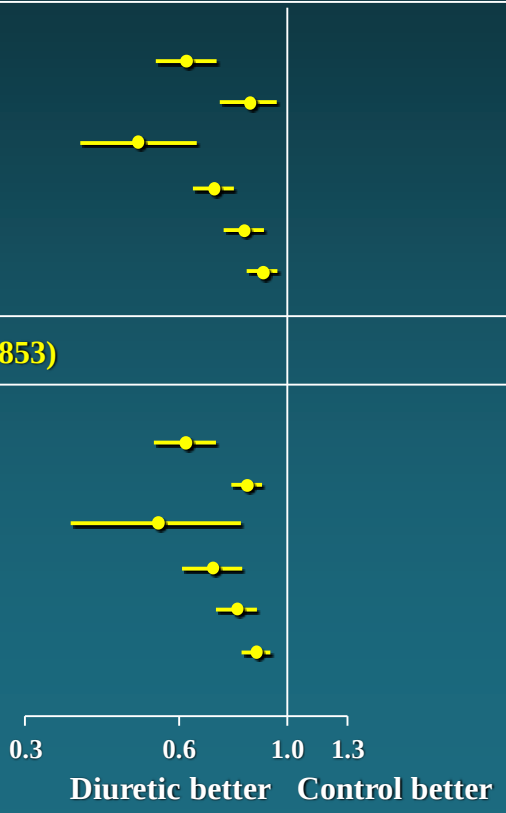
- Base recommendations on properly conducted studies,identified by an extensive review of the literature
- Highest priority to data from RCTs
- Also consider well conducted meta-analyses of RCTs (but not network meta-analyses)
- To recognize that RCTs cannot address many important questions, which can be addressed by observational or registry-based studies
- To grade the level of scientific evidence and the strength of recommendations
- To recognize that there are circumstances that cannot be ignored in which there is inadequate/no evidence.We resort to pragmatic expert opinion and endeavour to explain the rationale

Treatment Titration at 2 Years in HYVET



Risk Reduction of Various Outcomes in Trials with Diuretics

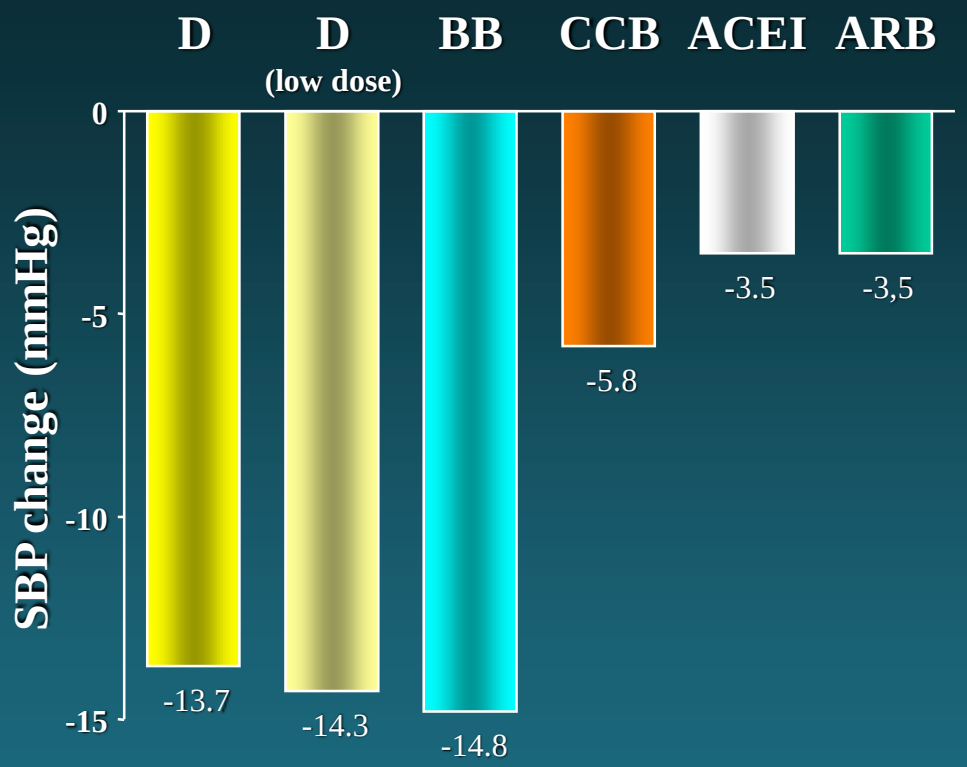
Outcome	Trials (n)	Outcome risk (% in 5 years)	SBP/DBP Δ (mmHg)	RR (95% CI)	RR (95% CI)	Absolute Risk Reduction 1000 pts/5 years	NNT 5 years
Primary analysis (events = 14004)							
Stroke	11	4.3	-11.9/-5.5	0.63 (0.55-0.72)		-15	67
CHD	12	4.2	-11.9/-5.5	0.84 (0.74-0.95)		- 7	148
HF	6	3.8	-13.7/-5.2	0.51 (0.39-0.66)		-17	60
Stroke + CHD + HF	8	8.6	-13.9/-5.7	0.71 (0.65-0.78)		-24	41
CV Death	12	4.4	-11.9/-5.5	0.82 (0.75-0.90)		- 8	129
All-cause Death	12	7.8	-11.9/-5.5	0.89 (0.83-0.95)		- 8	118
Secondary analysis (events = 21853)							
Stroke	19	5.3	-11.4/-5.2	0.63 (0.54-0.72)		-19	53
CHD	21	4.6	-11.4/-5.2	0.83 (0.77-0.89)		- 8	128
HF	12	4.4	-11.5/-4.7	0.55 (0.37-0.80)		-18	54
Stroke + CHD + HF	14	10.6	-12.1/-5.1	0.71 (0.62-0.81)		-30	33
CV Death	20	4.6	-11.3/-5.2	0.79 (0.72-0.87)		-10	104
All-cause Death	20	8.2	-11.3/-5.2	0.87 (0.81-0.92)		-11	95

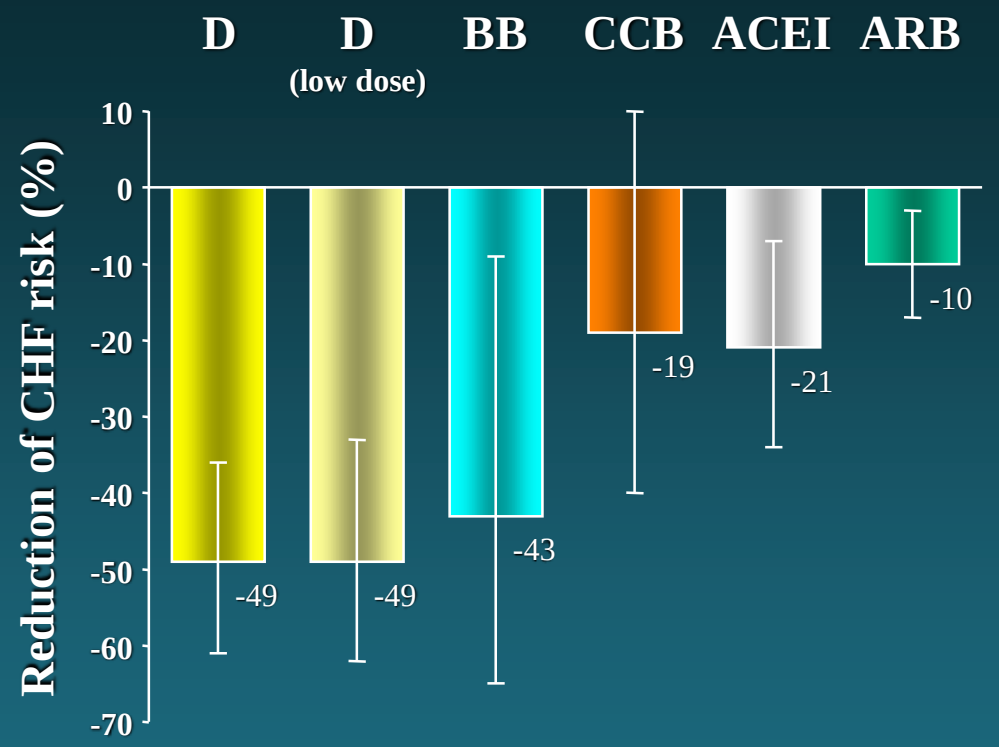


19524 M

Thomopoulos et al., J Hypertens 2015; 33; 195

BP and CHF reduction with different antihypertensive drugs vs control

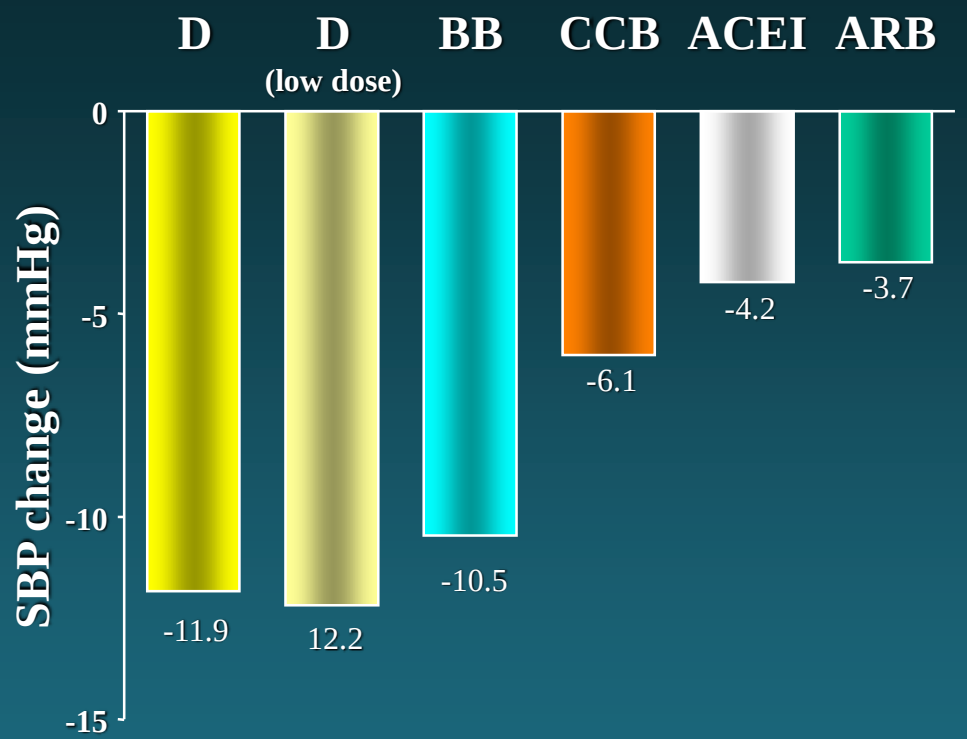


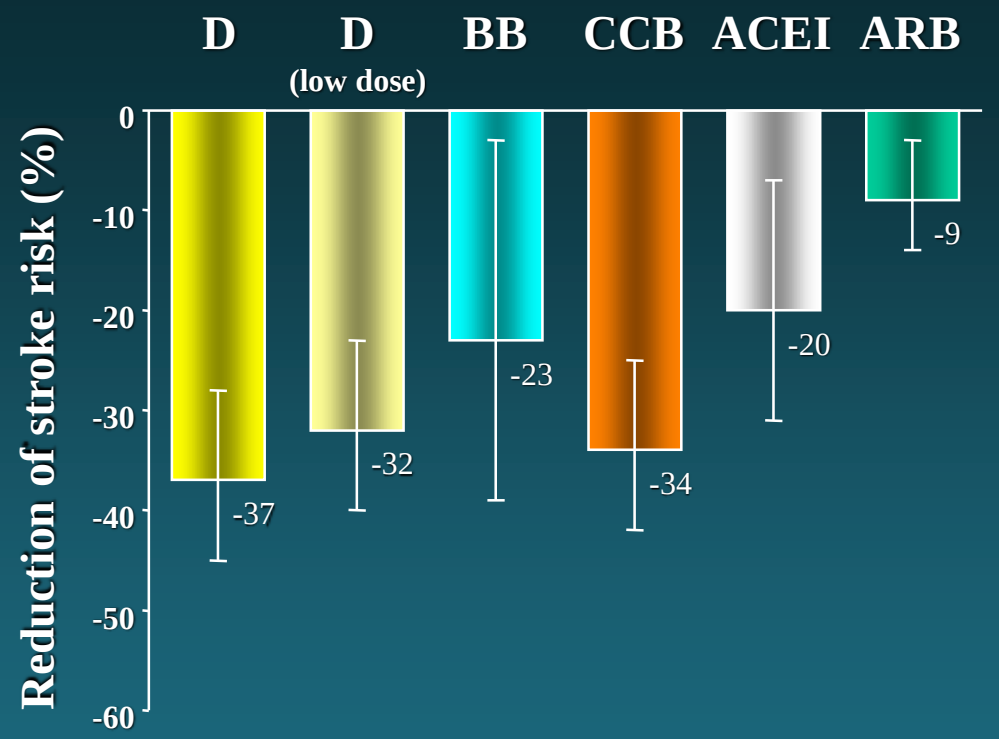


20374 M

Thomopoulos et al., J Hypertens 2015; 33: 195

BP and stroke reduction with different antihypertensive drugs vs control



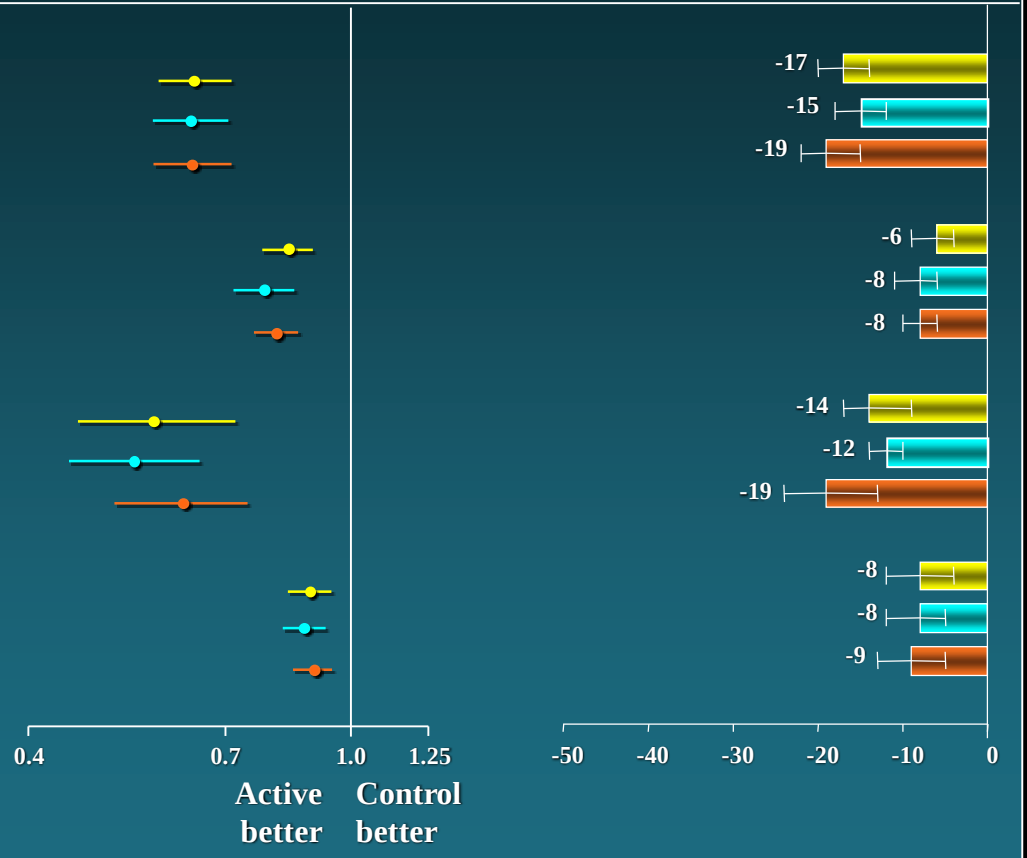


20375 M

Thomopoulos et al., J Hypertens 2015; 33: 195

Relative and Absolute Risk Reduction of Various Outcomes in Trials of BP Lowering

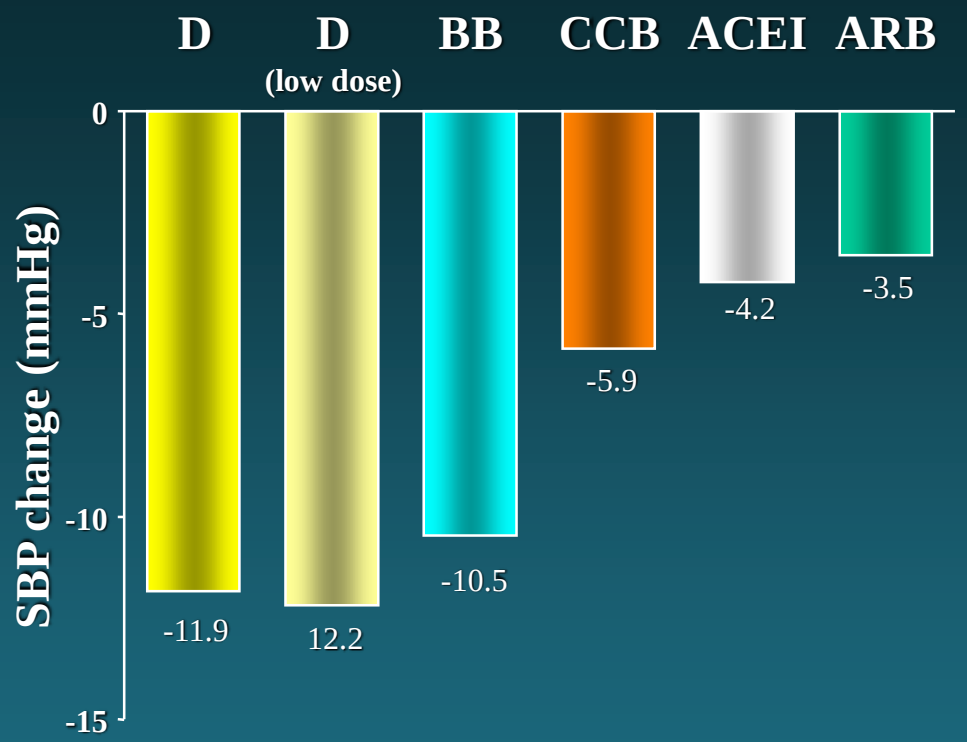
Outcome	Trials (n)	Difference SBP/DBP (mmHg)
Stroke		
A. Intentional	38	-8.4/-4.4
B. Intent. HT	31	-9.0/-4.8
C. Intent + Non-Intent	54	-6.6/-3.5
CHD		
A. Intentional	42	-8.6/-4.4
B. Intent. HT	35	-9.0/-4.8
C. Intent + Non-Intent	58	-6.7/-3.4
HF		
A. Intentional	24	-9.2/-4.3
B. Intent. HT	20	-10.6/-4.8
C. Intent + Non-Intent	36	-6.0/-2.9
All-cause Death		
A. Intentional	46	-8.6/-4.4
B. Intent. HT	37	-9.0/-4.8
C. Intent + Non-Intent	66	-6.7/-3.5

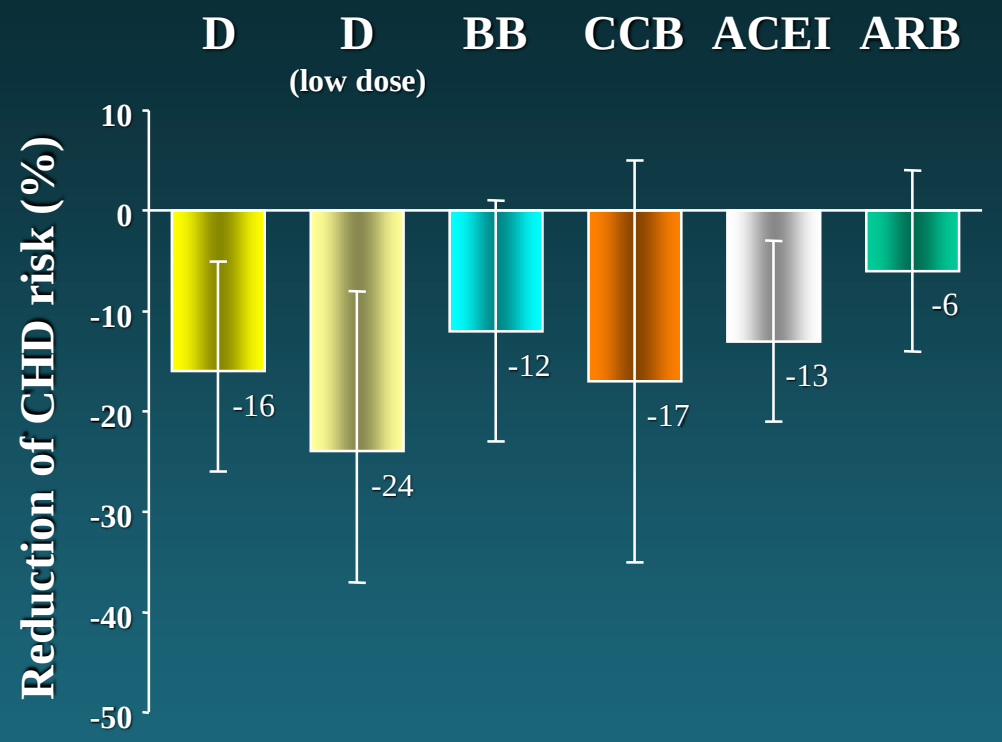


19674 M

Zanchetti et al., Circ Res 2015; 116: 1058

BP and CHD reduction with different antihypertensive drugs vs control





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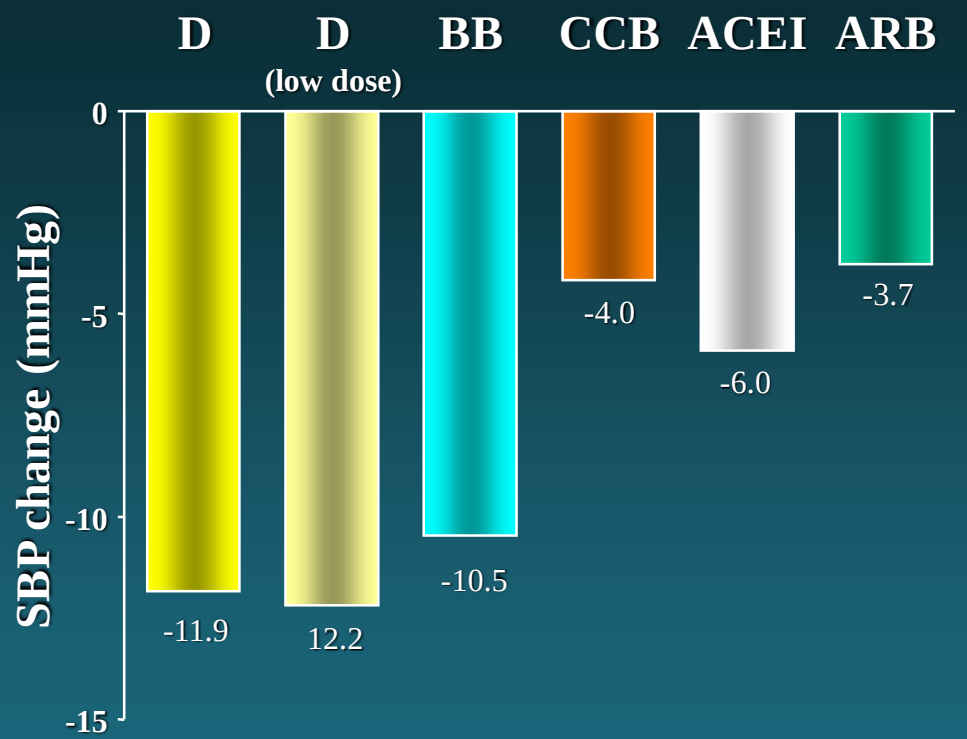
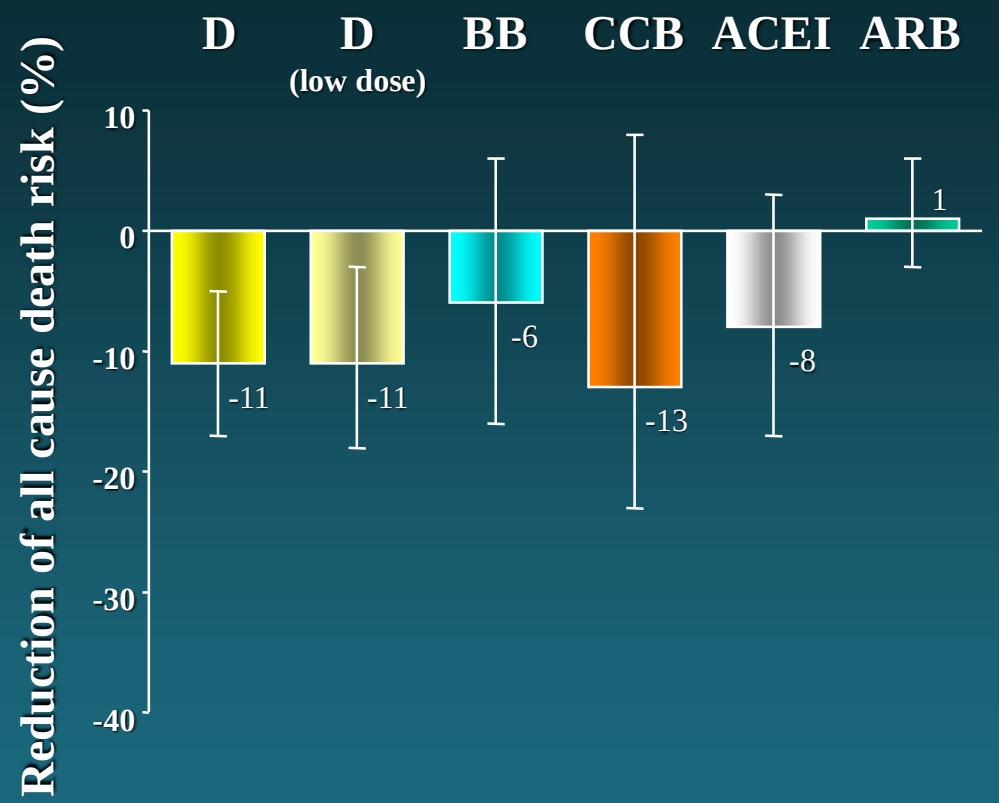
Thomopoulos et al., J Hypertens 2015; 33: 195

BP and all cause death reduction with different antihypertensive drugs vs control





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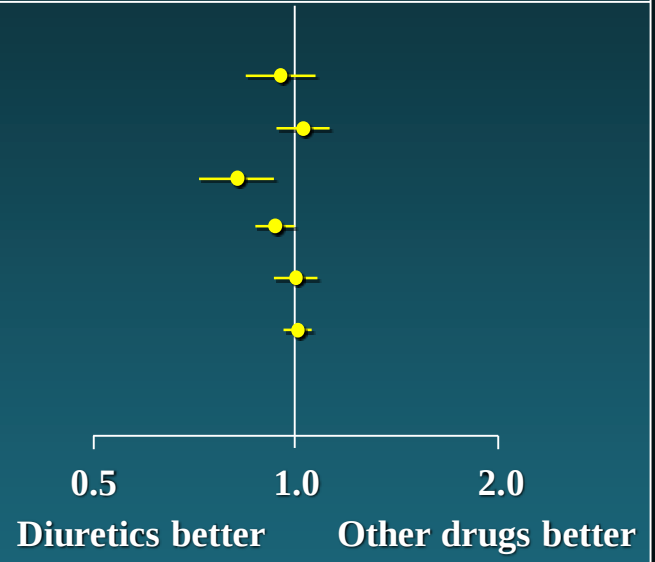
Thomopoulos et al., J Hypertens 2015; 33: 195

BP-lowering Treatment Based on Diuretics vs All Other Drug Classes

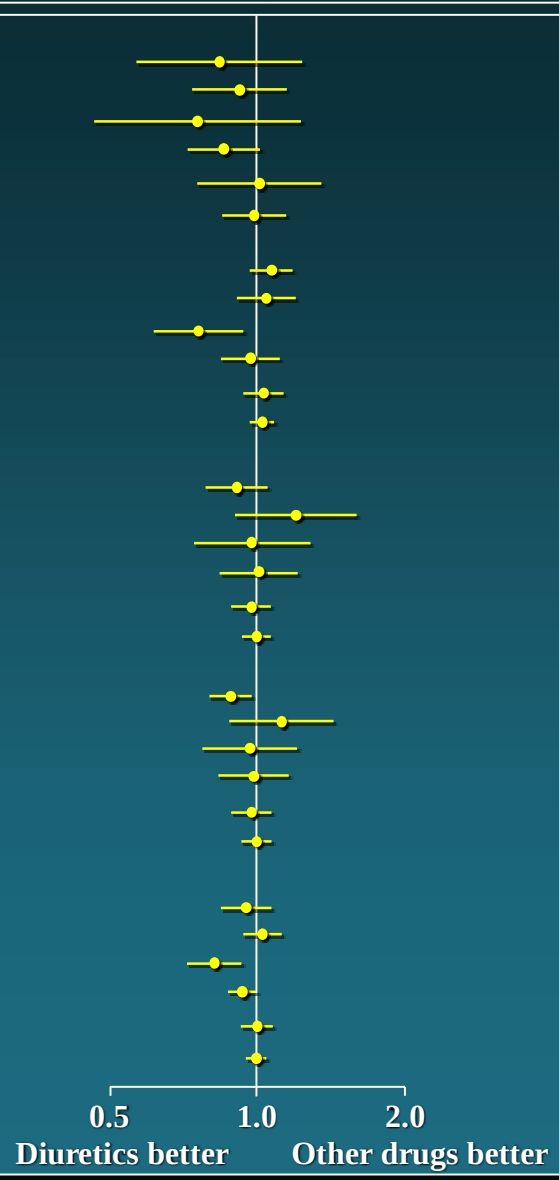
Outcome	Trials (n)	Difference SBP (mmHg)	RR	RR (95% CI)
Stroke	21	-0.78	0.96	
CHD	21	-0.78	1.03	
HF	12	-0.80	0.83	
Stroke + CHD + HF	14	-0.78	0.94	
CV Death	17	-0.83	1.01	
All-cause Death	21	-0.43	1.02	



Thomopoulos et al, J Hypertens 2015; 33: 1321

BP-lowering Treatment Based on Diuretics vs Other Drugs

	Outcome	Trials (n)	Difference SBP (mmHg)	RR
vs Beta-Blockers	Stroke	7	-0.48	0.85
	CHD	7	-0.48	0.93
	HF	2	0.40	0.76
	Stroke + CHD + HF	4	-1.82	0.86
	CV Death	5	-0.49	1.03
	All-cause Death	7	-0.44	0.99
vs Calcium Antagonists	Stroke	8	-0.23	1.08
	CHD	8	-0.23	1.06
	HF	7	-0.25	0.78
	Stroke + CHD + HF	7	-0.25	0.98
	CV Death	7	-0.28	1.04
	All-cause Death	8	-0.23	1.03
vs ACE-Inhibitors	Stroke	5	-1.90	0.91
	CHD	5	-1.90	1.20
	HF	2	-1.98	0.97
	Stroke + CHD + HF	2	-1.98	1.02
	CV Death	5	-1.90	0.98
	All-cause Death	5	-1.90	1.01
vs RAS Blockers	Stroke	6	-1.82	0.90
	CHD	6	-1.82	1.13
	HF	3	-1.89	0.96
	Stroke + CHD + HF	3	-1.89	0.99
	CV Death	5	-1.90	0.98
	All-cause Death	6	-1.82	1.01
vs All Other Drug Classes	Stroke	21	-0.78	0.96
	CHD	21	-0.78	1.03
	HF	12	-0.80	0.83
	Stroke + CHD + HF	14	-0.78	0.94
	CV Death	17	-0.83	1.01
	All-cause Death	21	-0.43	1.02



Thomopoulos et al, J Hypertens 2015; 33: 1321