« Harmonization of the ACC/AHA and ESC/ESH blood pressure/hypertension guidelines: Comparisons/reflections/recommendations »

Whelton/Carey/Mancia/Kreutz/Bundy/Williams
JACC, in press

BP classification in US and EU Hypertension (HT) GLs (*US GLs:unified as pre-HT)

BP (mmHg)	US (2003)/EU(2007-2013-2018)	US (2017)
< 120/80	Optimal	Normal
120-129 / 80-84	Normal*	Elevated
130-139 / 85-89	High normal*	Grade 1 HT
140-159 / 90-99	Grade 1 HT	Grade 2 HT
160-179 / 100-110	Grade 2 HT	
> 180/110	Grade 3 HT	

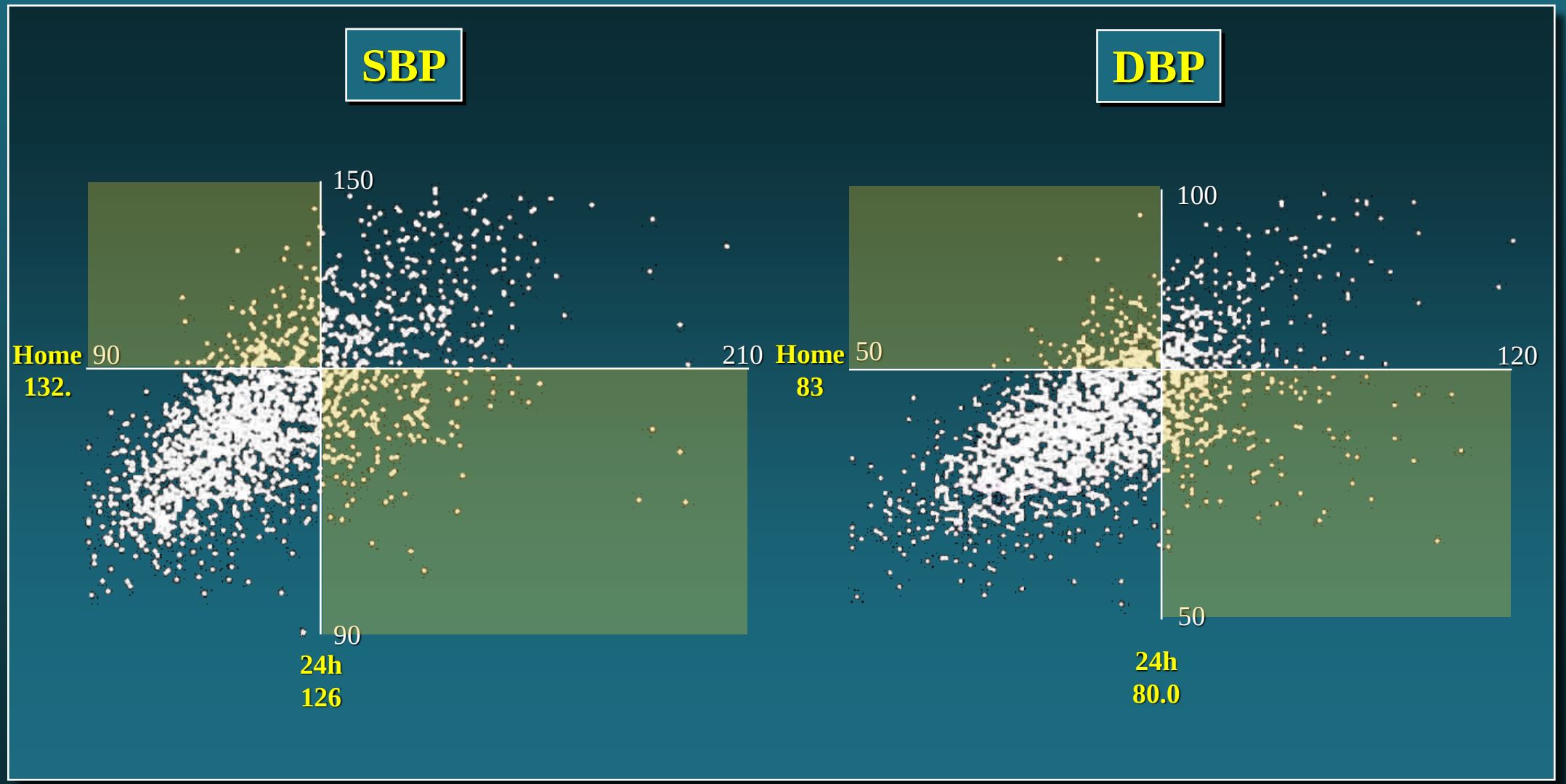
BP classification by ACC-AHA GLs
Possible consequences

- Elimination of Grade 3 HT : Unnecessary (grading the HT severity useful)
- Downshift of Grade 2 HT (>-140 rather than 160mmHg): Unnecessary (pts treated anyway)
- High normal BP (130mmHg) now called Grade 1 HT: More pts defined as HT& but many of them not treated
- Normal BP (120-129mmHg) now called elevated: Paradoxical/potential harm(see old pts)

Use of Out-of-office BP

- Wider use recommended by both GLs
- In US GLs preference to Home BP while in EU GLs mention of specific pros/cons and Home &ABP regarded as complementary

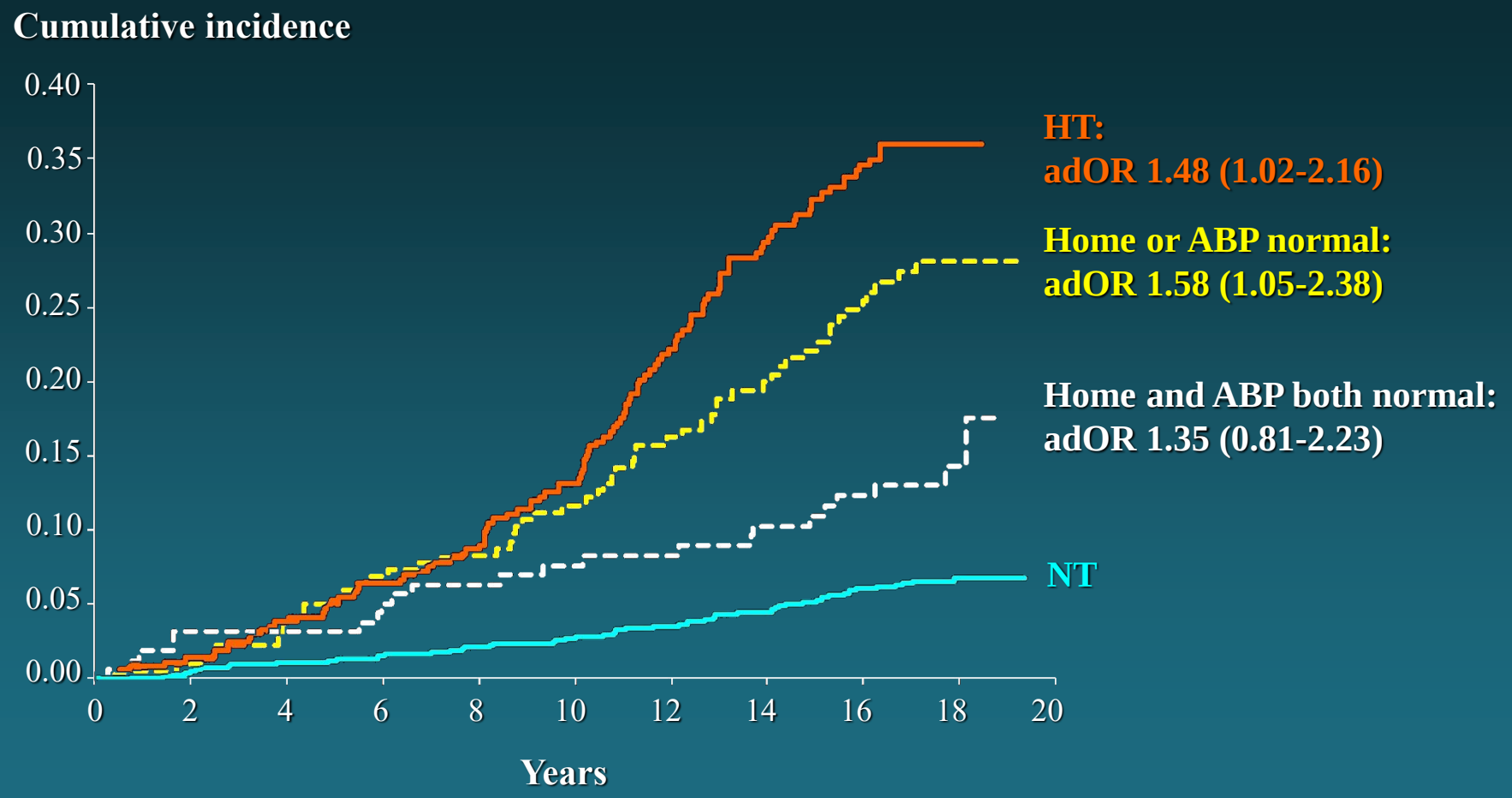
Relationship between 24h and Home BP in PAMELA



19878 = 18395 M mod

Mancia et al., Hypertension 2006; 47: 846; Mancia et al., unpublished data

All cause mortality in WCH diagnosed by normality of one or both 24h and home BP

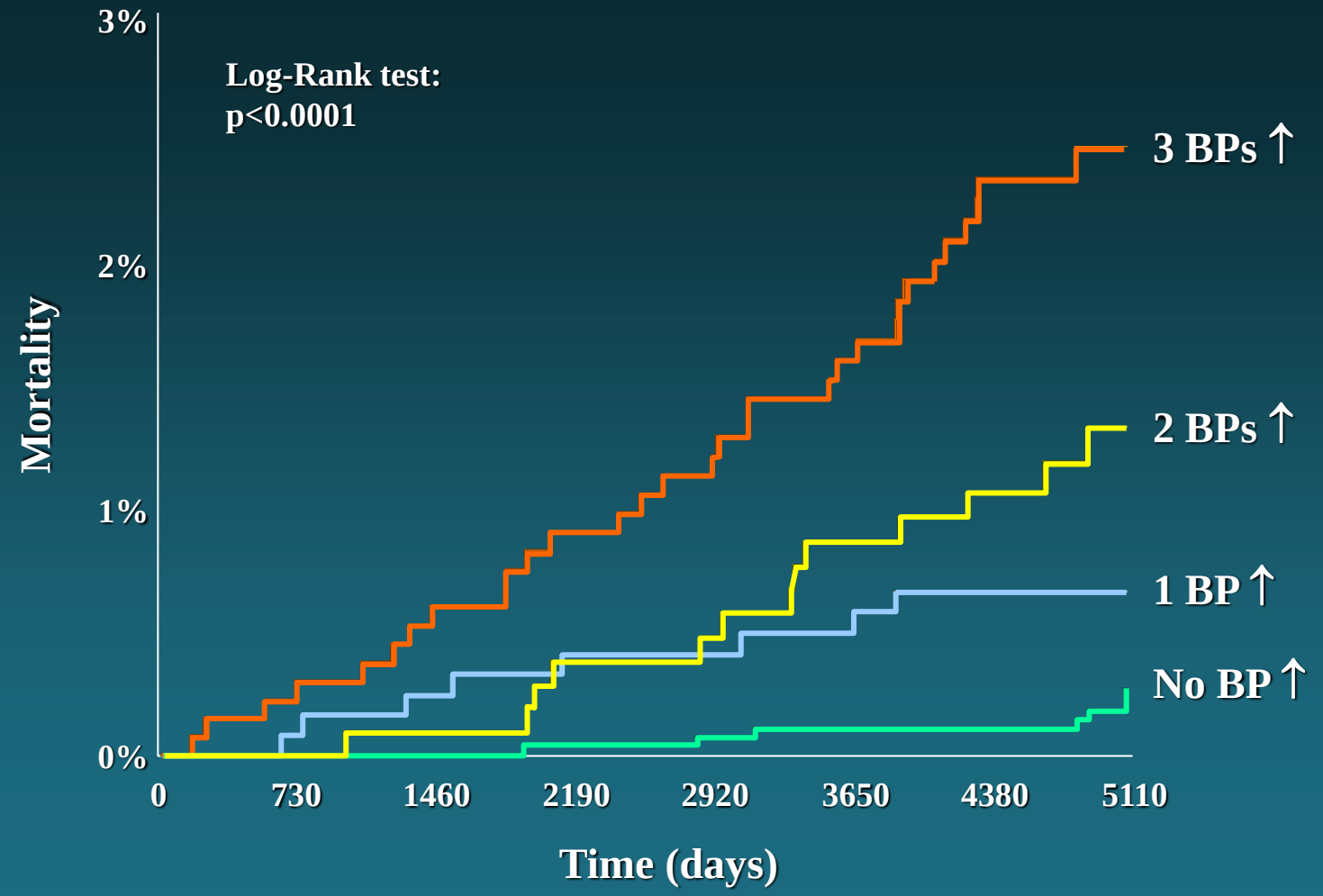


21188 = 20640 M mod

Mancia et al. Hypertension 2013,62,168

Progressive Increase in CV Mortality

(age/gender adjusted data from 0 to 3 BP elevations [office/home/24h mean])



Mancia G., Hypertension 2006, Mancia G., Hypertension 2007

Use of Out-of-office BP

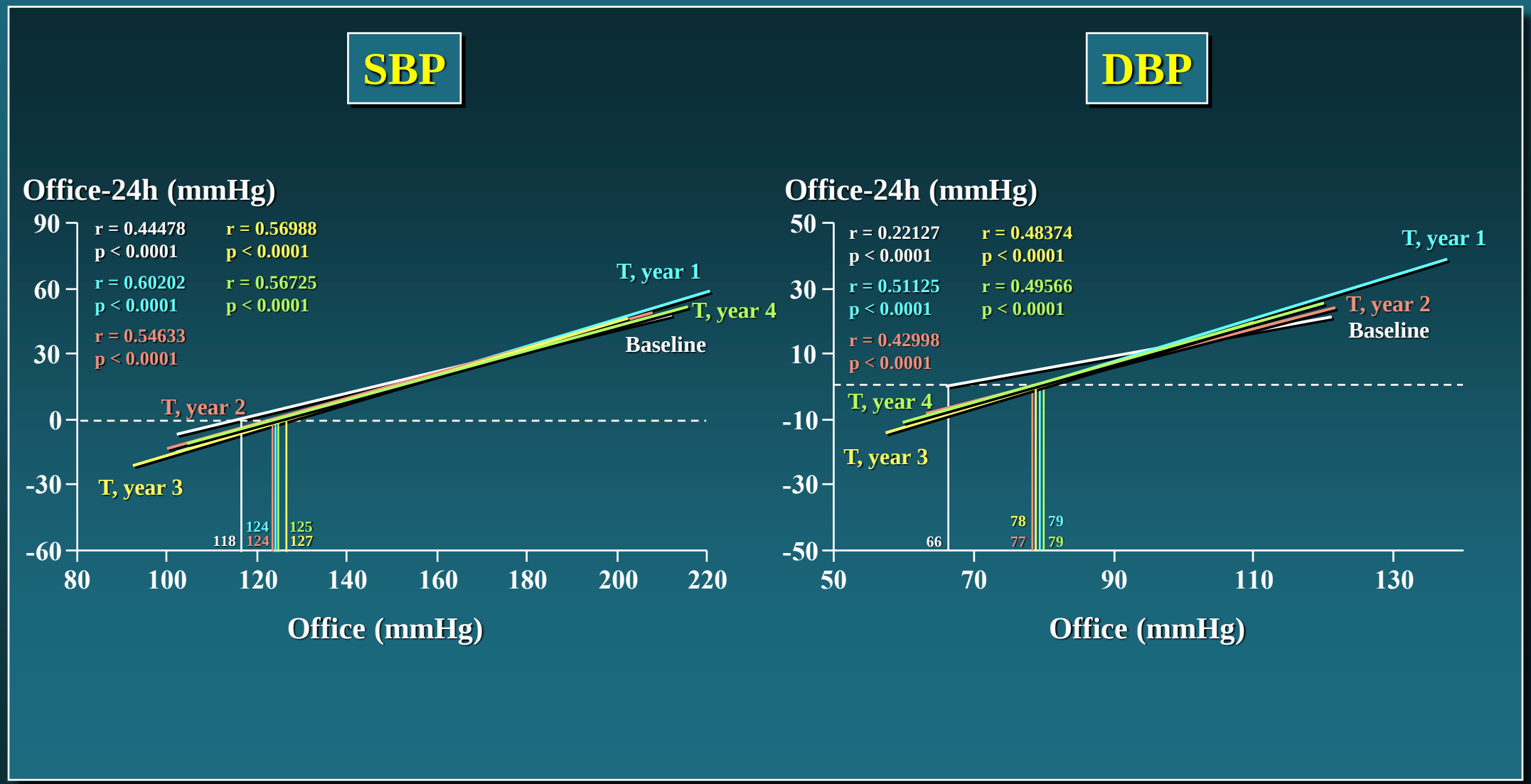
- Wider use recommended by both GLs
- In US GLs preference to Home BP while in EU GLs mention of specific pros/cons and Home &ABP regarded as complementary
- Target 24h BP lower in US than EU GLs (125/75 vs 130/80mmHg)
- Limitations of the evidence only mentioned by EU GLs

Corresponding Values of SBP/DBP for Clinic, HBPM, Daytime, Nighttime, and 24-Hour ABPM Measurements

Clinic	HBPM	Daytime ABPM	Nighttime ABPM	24-Hour ABPM
120/80	120/80	120/80	100/65	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/85	120/70	130/80
160/100	145/90	145/90	140/85	145/90

ABPM indicates ambulatory blood pressure monitoring; BP, blood pressure; DBP diastolic blood pressure; HBPM, home blood pressure monitoring; and SBP, systolic blood pressure.

Relationship between Office BP and Office-24h BP Δ in ELSA



16350 M

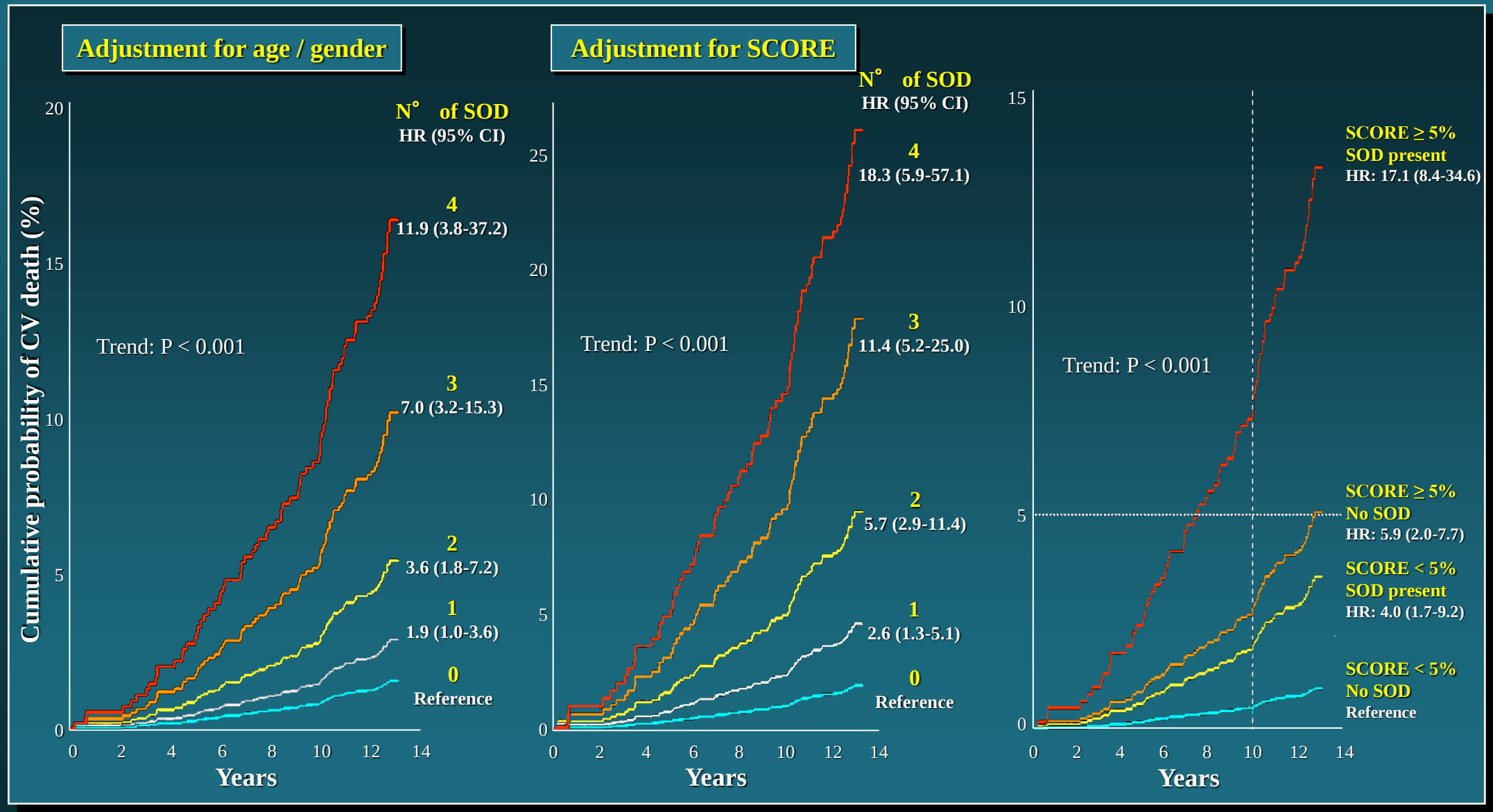
MANCIA ET AL, UNPUBLISHED

EU &US GLs differences on assessment of organ damage

- Agreement on need to quantify CV risk but approach and risk factors listed somewhat different (e.g. HR in EU GLs)
- For EU(but not US) GLs HT-related organ damage most important

- Fundamental for identification of high CV risk
- Useful for drug (s) choice
- Marker of treatment benefit,e.g.LVH/UACR reduction

Cumulative Probability of CV Death according to Presence / Number of Organ Damage

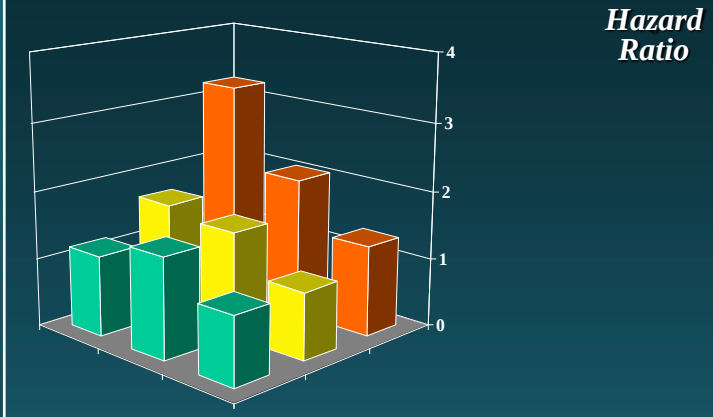


20184 M LVH - Atherosclerotic plaques - PWV >12 m/s - UACR ≥ 90th percentile

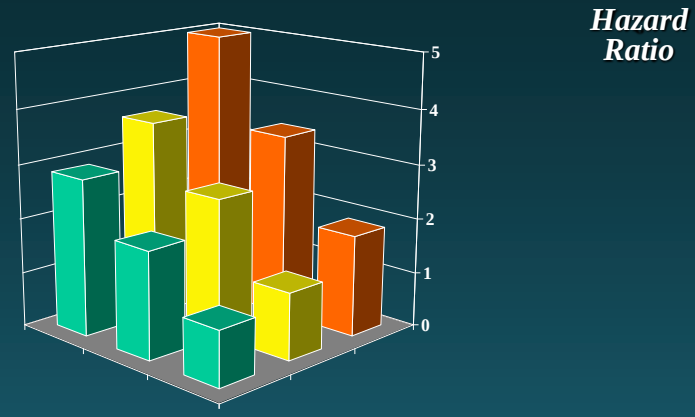
Sehestedt T et al., Eur Heart J 2010; 31: 883-891

Combined Effects of Albuminuria and eGFR Levels at Baseline on the Risk for Adverse Outcomes in ADVANCE

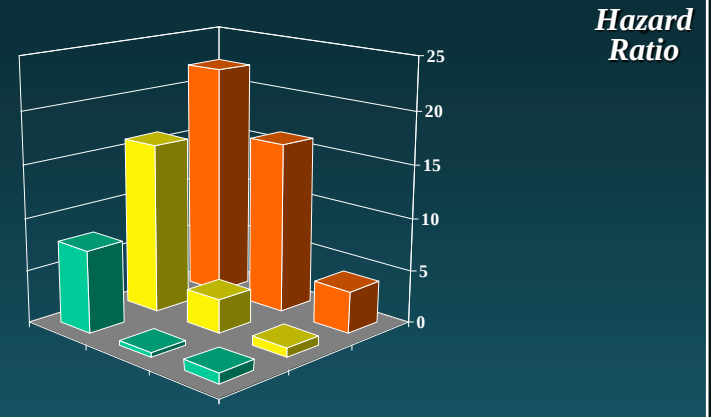
Cardiovascular events



Cardiovascular death

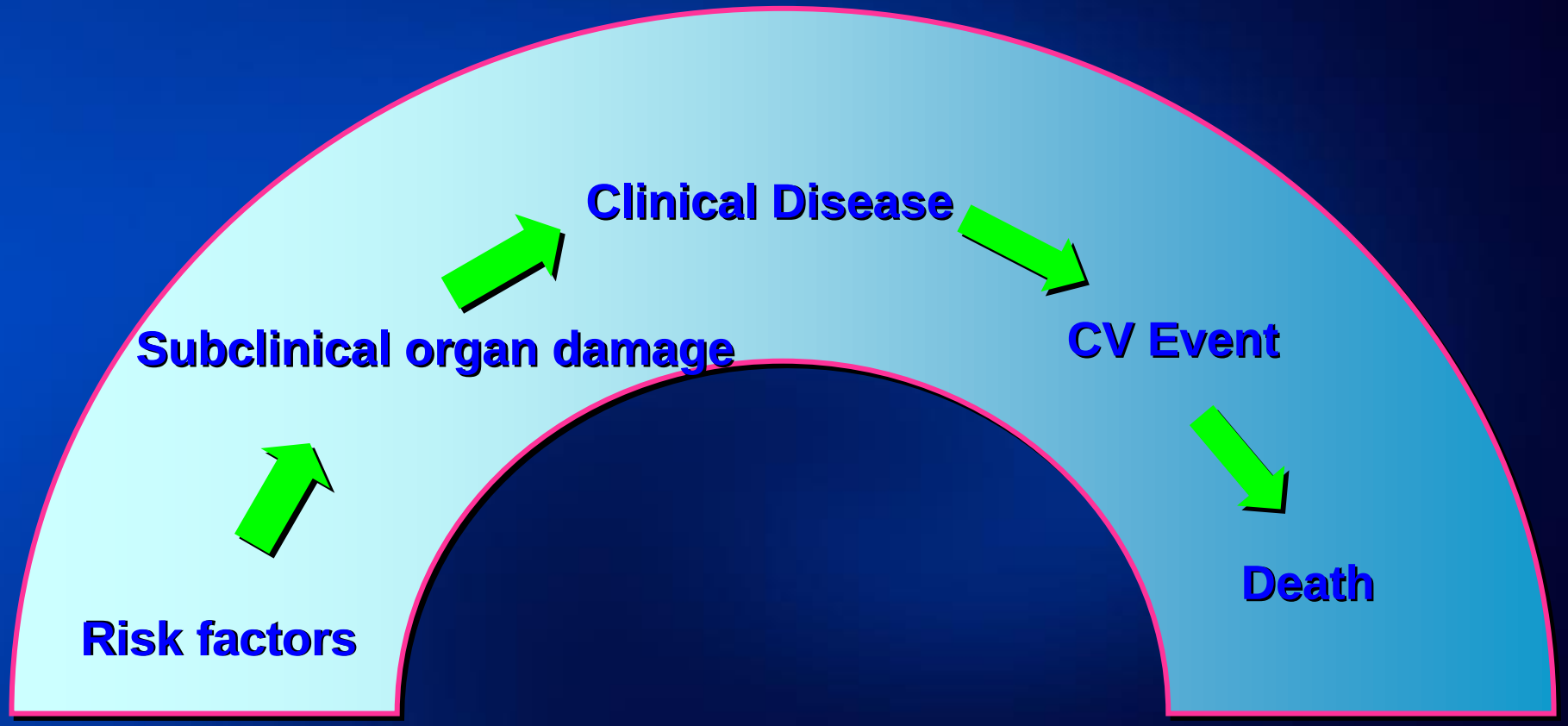


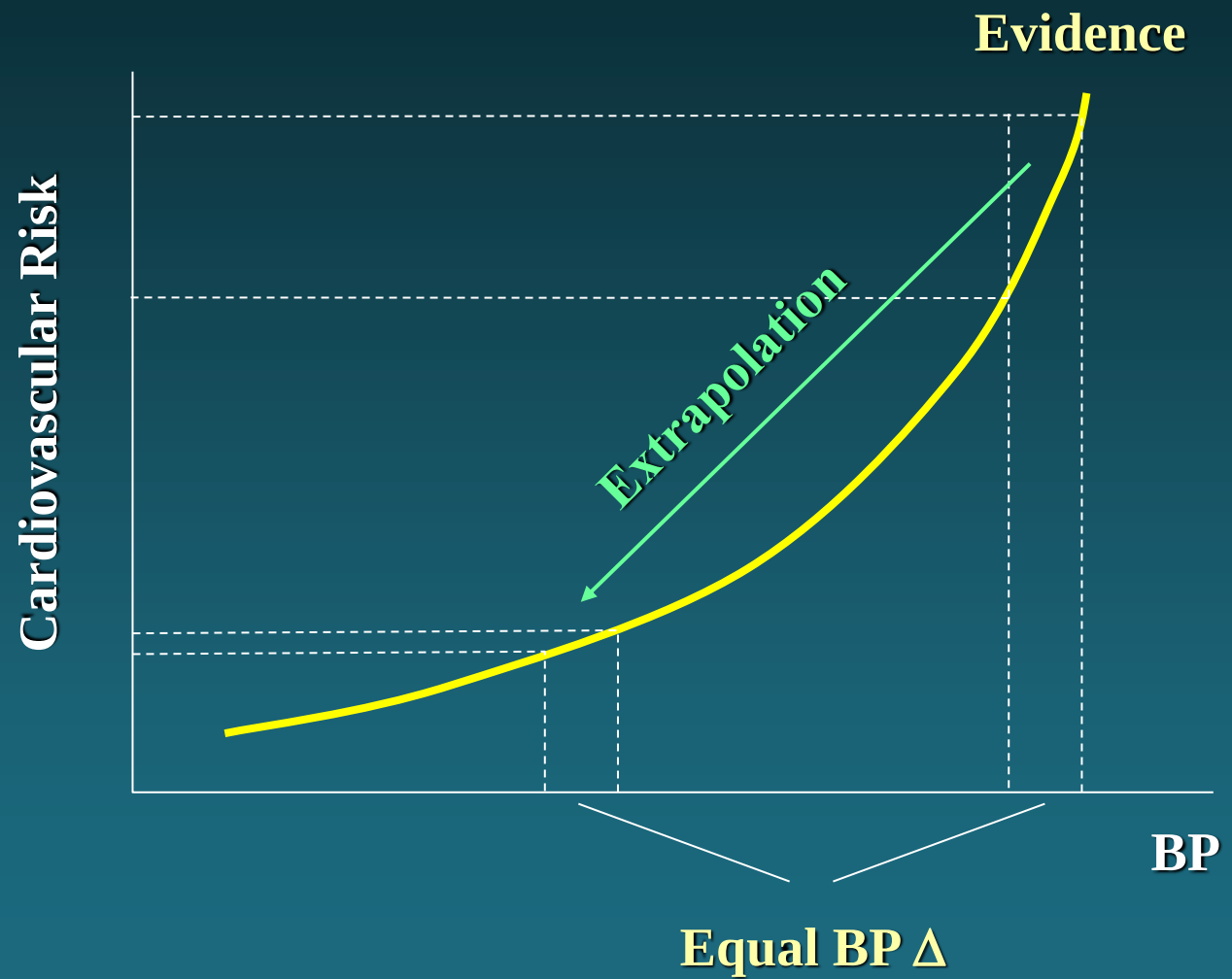
Renal events



14865 M

Ninomaya, Mancia,Chalmers, J Am Soc Nephrol 2009; 20: 1813


Clinical Disease
Subclinical organ damage
CV Event
Death
Risk factors

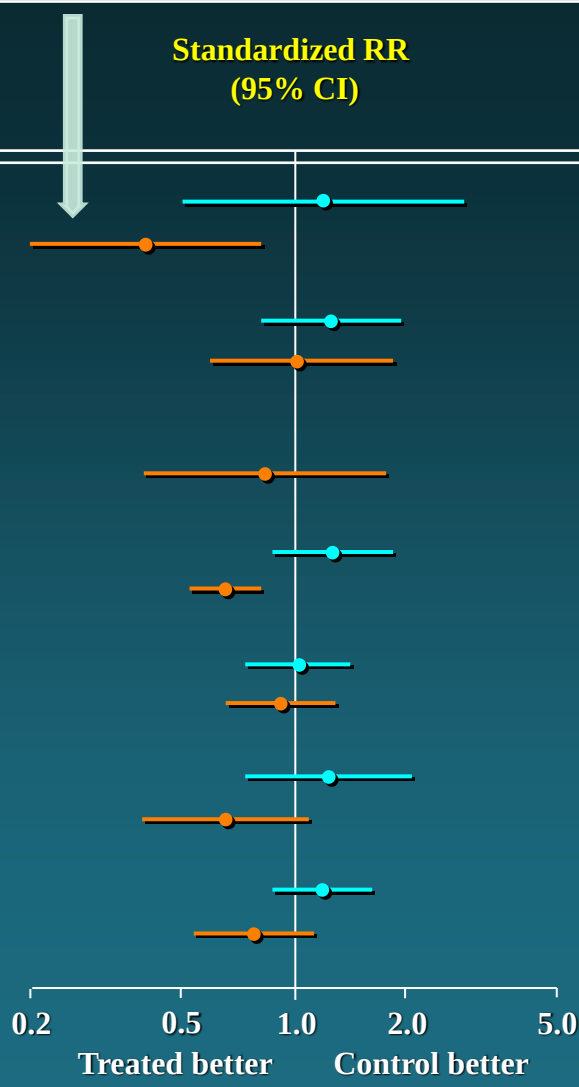

Evidence
Cardiovascular Risk
Extrapolation
BP
Equal BP Δ

Summary of office BP thresholds for treatment

Age 18-65 years	Age 65-79 years	Age ≥ 80 years	Very high risk
≥ 140/90 mmHg	≥ 140/90 mmHg	≥ 160/90 mmHg	≥ 130/85 mmHg can be considered
IA	IA	IA	IIbA
Target BP:			
< 130/80 mmHg	< 140/80 mmHg	< 140/80 mmHg	< 130/80 mmHg

Relative risk of morbidity and mortality outcomes in individuals with high-normal or normal BP: comparison of individuals at low–moderate and high–very high CV risk

Outcome	CV risk	Trials (n)	Standardized RR (95% CI)	P-value interaction
Stroke	L-M	4	1.20 (0.51-2.78)	0.006
	H-VH	8	0.40 (0.20-0.81)	
CHD	L-M	4	1.25 (0.82-1.92)	0.089
	H-VH	6	1.00 (0.60-1.84)	
HF	L-M	1	-	-
	H-VH	5	0.82 (0.38-1.81)	
Stroke + CHD	L-M	3	1.27 (0.88-1.81)	<0.001
	H-VH	8	0.65 (0.52-0.80)	
Stroke + CHD + HF	L-M	5	1.02 (0.73-1.39)	0.32
	H-VH	6	0.91 (0.66-1.29)	
CV Death	L-M	3	1.23 (0.74-2.06)	0.001
	H-VH	6	0.66 (0.40-1.09)	
All Death	L-M	10	1.18 (0.88-1.60)	0.016
	H-VH	6	0.77 (0.54-1.13)	



20355 M

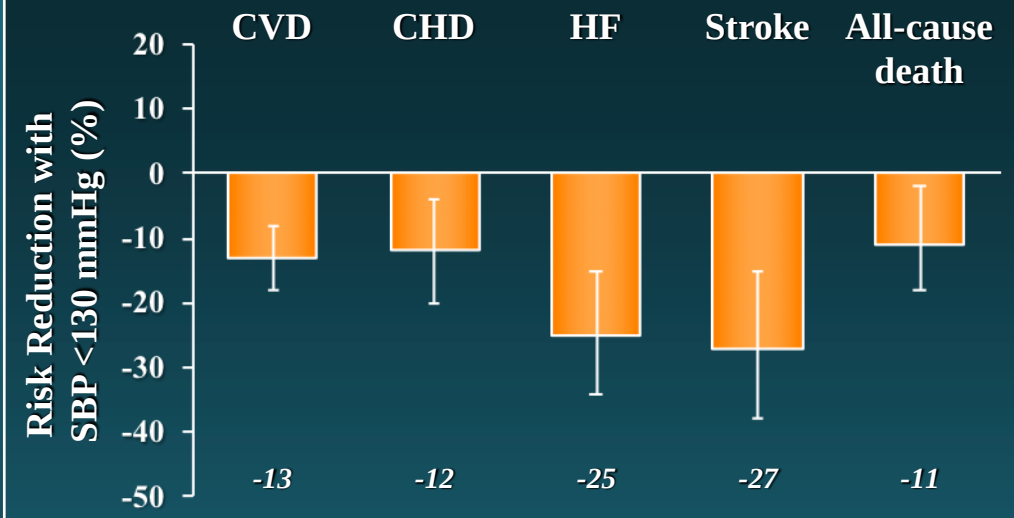
Thomopoulos et al., J Hypertens 2017; 35: 2150

High normal BP and antihypertensive drugs

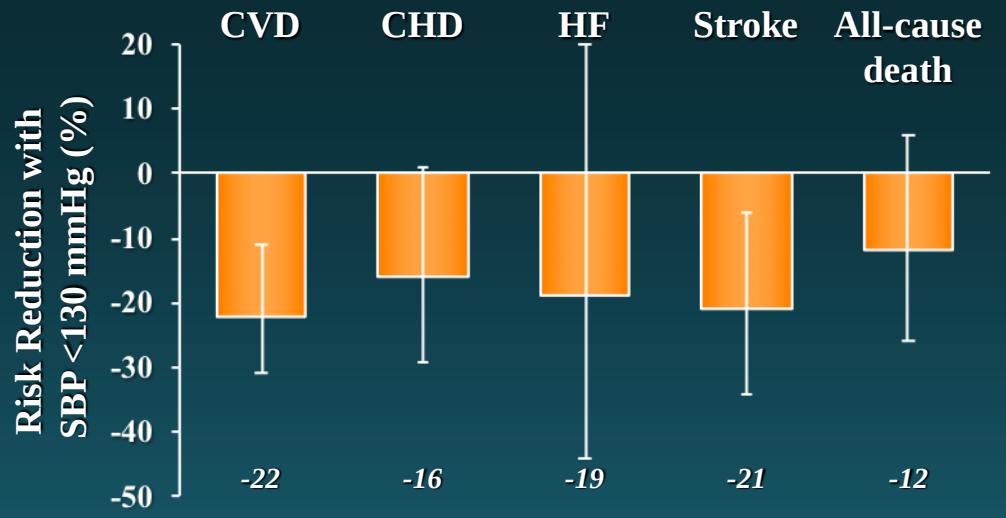
- ESC/ESH GLs: only in pts with history of CV events
- ACC/AHA GLs: recommended if 10yr Framingham risk score is >10%
- In the elderly this cutoff value is reached just because of the advanced age
- Labelling high normal BP pts as «grade 1 hypertensives» may stimulate most doctors and patients to use drugs

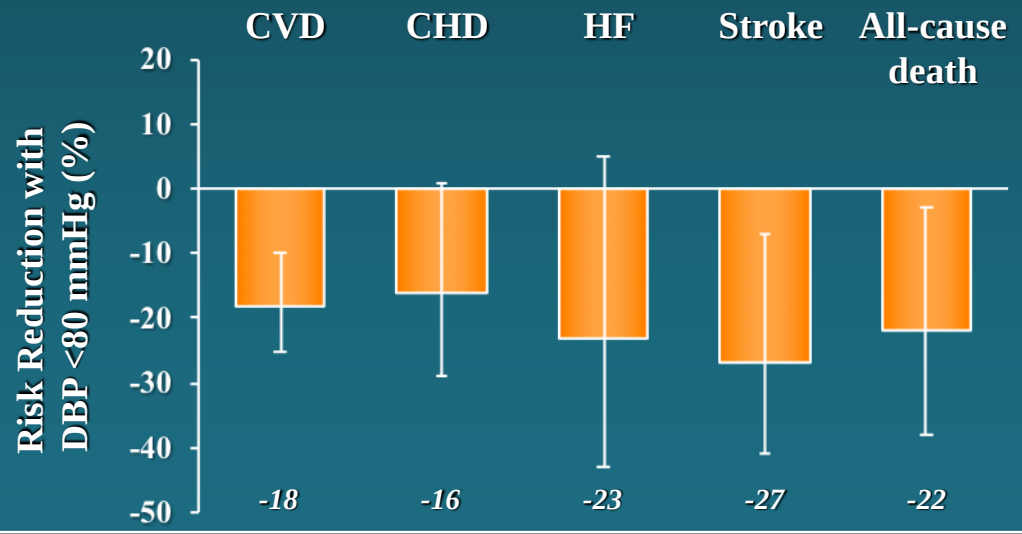
Risk reduction achieved by lowering SBP to <130 or DBP to <80 mmHg vs higher BP values in RT-based meta-analyses

Ettehad et al. (Lancet, 2015)



Thomopoulos et al. (J Hypertens, 2016)





Thomopoulos et al. (J Hypertens, 2016)

20663 M

Redrawn by Mancia, 2019

BP Thresholds for and Goals of Pharmacological Therapy in Patients With Hypertension According to Clinical Conditions

Clinical Condition(s)	BP Threshold, mm Hg	BP Goal, mm Hg
General		
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; noninstitutionalized, ambulatory, community-living adults)	≥130 (SBP)	<130 (SBP)
Specific comorbidities		
Diabetes mellitus	≥130/80	<130/80
Chronic kidney disease	≥130/80	<130/80
Chronic kidney disease after renal transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥140/90	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

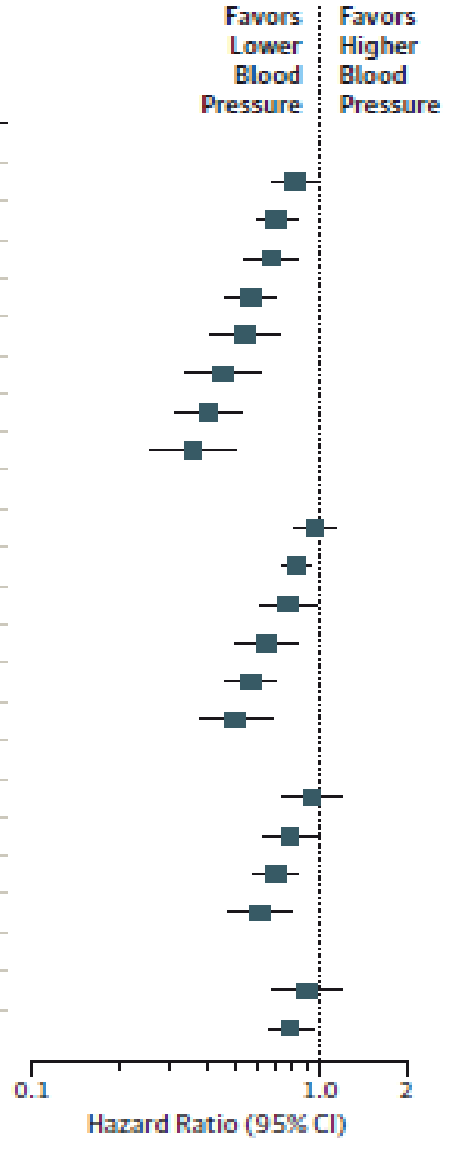
ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; and SBP, systolic blood pressure.

Office BP treatment targets in hypertensive patients - General Recommendations

	Class / Level
• The first objective of treatment should be to lower BP to <140/90 mmHg in all patients	IA
• Provided that treatment is well tolerated treated BP should be targeted to 130/80 mmHg or lower in patients aged <65years,unless with CKD	IA

Figure 3. Hazard Ratios and 95% CIs for Major Cardiovascular Disease Associated With More Intensive Reductions in Systolic Blood Pressure

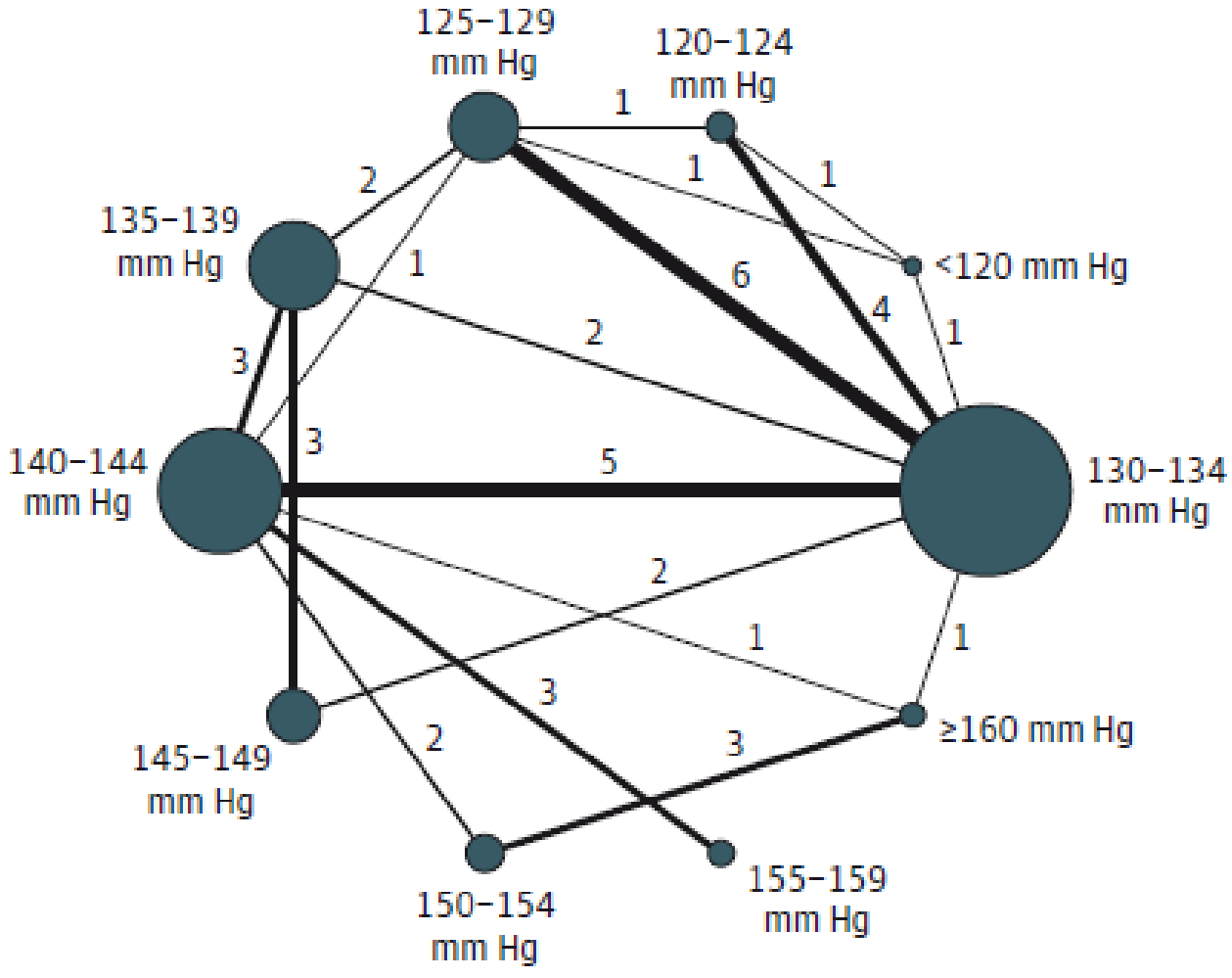
Mean Achieved Systolic Blood Pressure, mm Hg	Hazard Ratio (95% CI)
Reduction to 120-124	
120-124 vs 125-129	0.82 (0.67-0.97)
120-124 vs 130-134	0.71 (0.60-0.83)
120-124 vs 135-139	0.68 (0.55-0.85)
120-124 vs 140-144	0.58 (0.48-0.72)
120-124 vs 145-149	0.55 (0.42-0.72)
120-124 vs 150-154	0.46 (0.34-0.63)
120-124 vs 155-159	0.41 (0.32-0.54)
120-124 vs ≥160	0.36 (0.26-0.51)
Reduction to 130-134	
130-134 vs 135-139	0.96 (0.83-1.14)
130-134 vs 140-144	0.83 (0.74-0.94)
130-134 vs 145-149	0.78 (0.63-0.98)
130-134 vs 150-154	0.65 (0.51-0.85)
130-134 vs 155-159	0.58 (0.48-0.72)
130-134 vs ≥160	0.51 (0.39-0.69)
Reduction to 140-144	
140-144 vs 145-149	0.94 (0.74-1.20)
140-144 vs 150-154	0.79 (0.63-0.99)
140-144 vs 155-159	0.70 (0.60-0.84)
140-144 vs ≥160	0.62 (0.48-0.80)
Reduction to 150-154	
150-154 vs 155-159	0.90 (0.68-1.19)
150-154 vs ≥160	0.79 (0.66-0.94)



42 studies, n=144220

Bundy et al,
Jama, Cardiol
Doi:10.001/Jama

Figure 2. Network of Treatment Comparisons for Cardiovascular Disease and Mortality According to Achieved Systolic Blood Pressure Categories Among 42 Clinical Trials

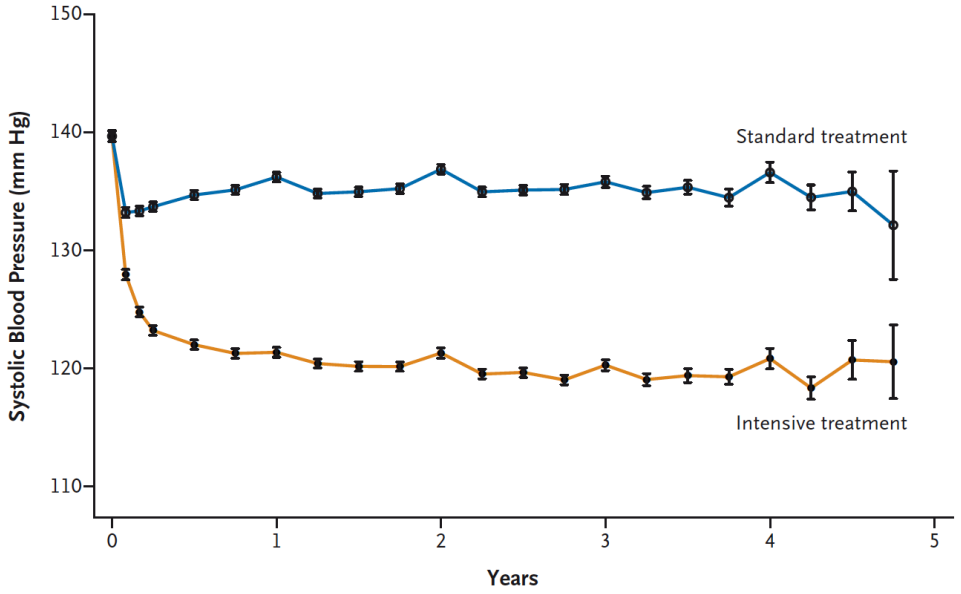


42 studies/n=144220

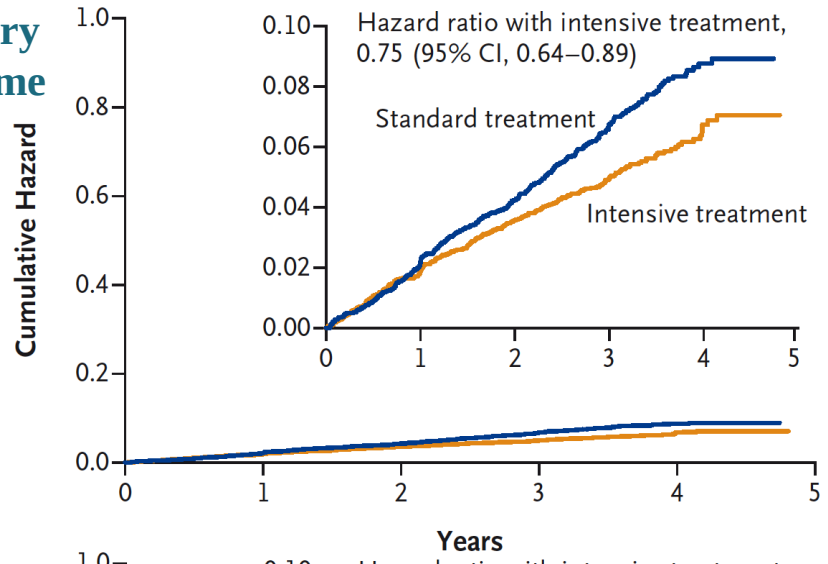
Bundy et al
JAMA, Cardiology
Doi:10.001/jama

SPRINT: SBP over the Trial and Outcomes/(On-T BP 134.6 vs 121.5/75.5 vs 67.2mmHg)

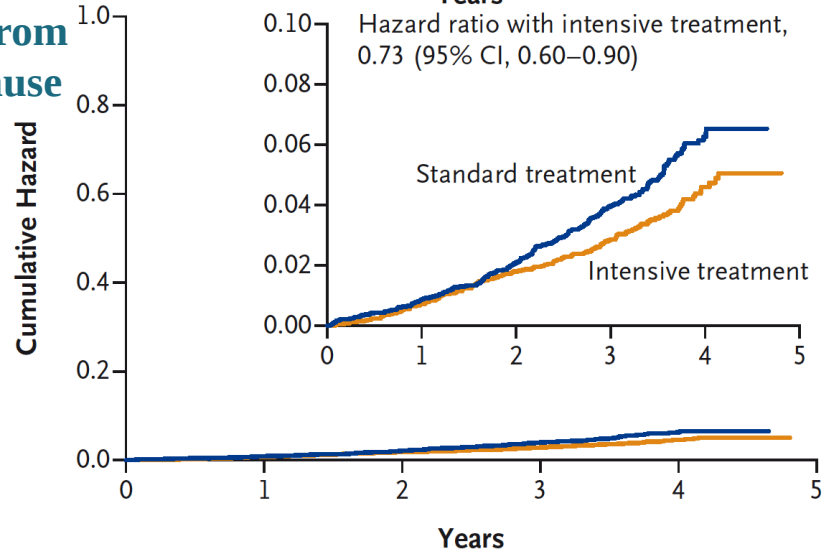
Systolic Blood Pressure



Primary Outcome



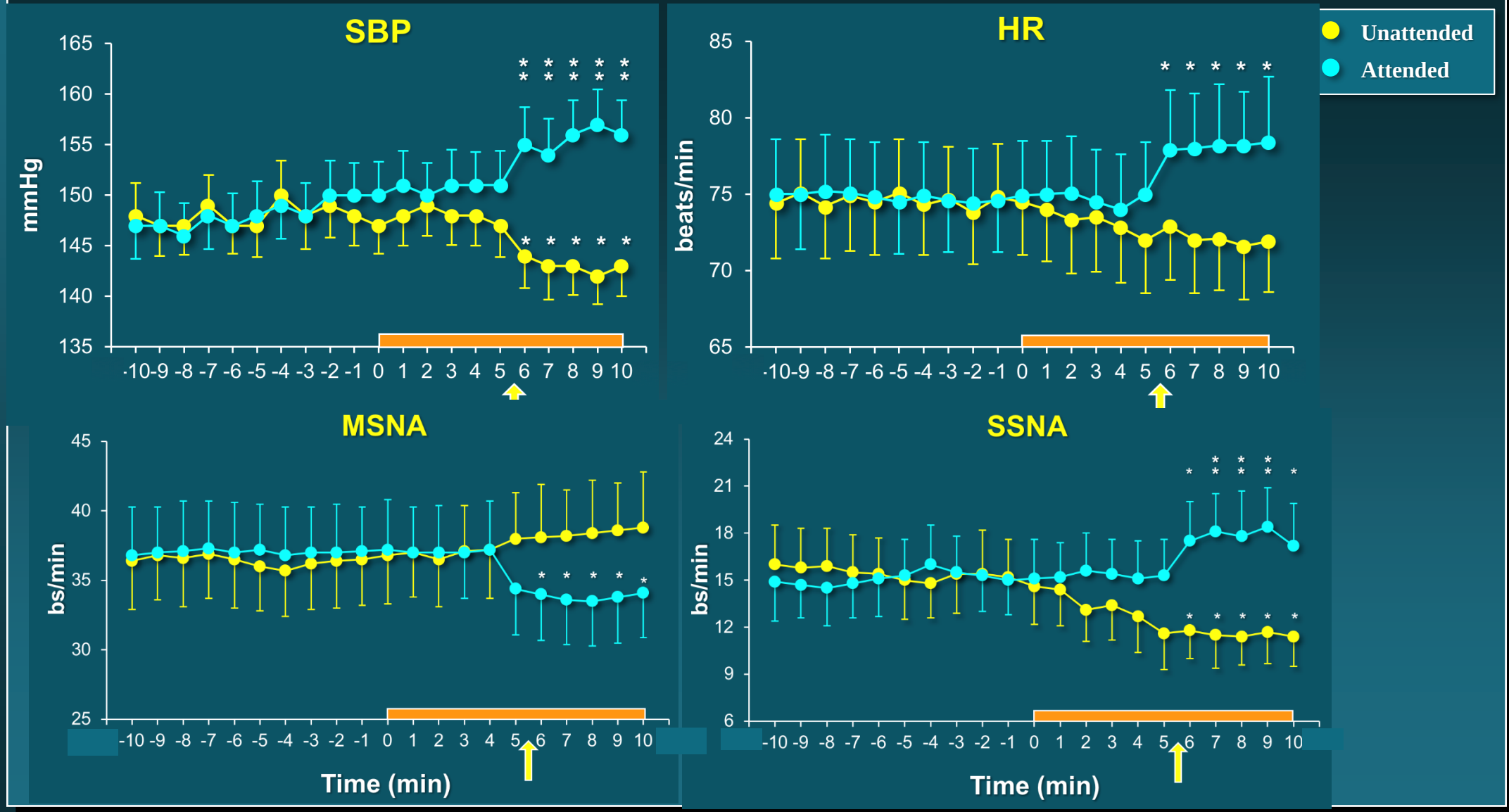
Death from Any Cause



19984a M

The SPRINT Research Group, NEJM 2015, 373,2103

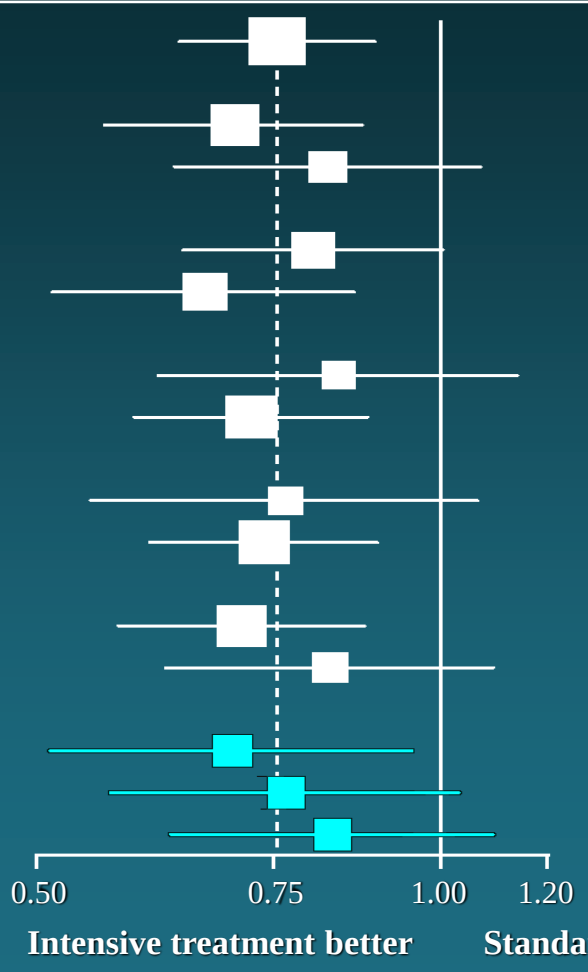
Beat-to-beat SBP, HR, MSNA and SSNA recorded before and during unattended and attended automatic BP measurement session



Grassi, Quarti-Trevano, Dell'Oro, Vanoli, Perseghin, Mancia, Hypertension 2021;
doi: 10.1161/HYPERTENSIONAHA.121.1765

SPRINT: Forest Plot of Primary Outcome according to Subgroups

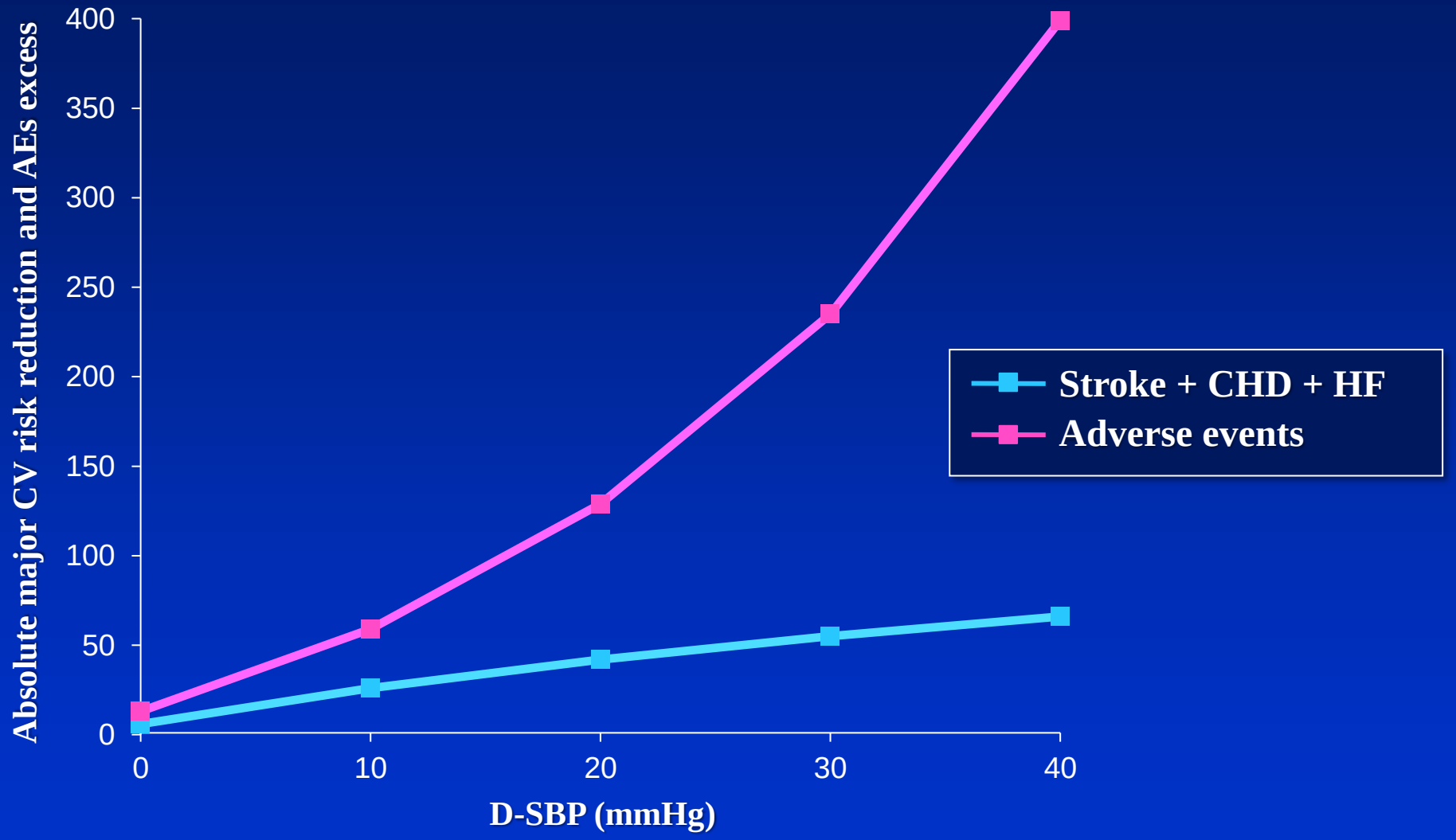
Subgroup	Intensive Treatment		Standard Treatment	Hazard Ratio (95% CI)	PValuefor Interaction
Overall	5.2	*% of patients*	6.8	0.75 (0.64–0.89)	
Previous CKD					
No	4.0		5.7	0.70 (0.56–0.87)	0.36
Yes	8.1		9.6	0.82 (0.63–1.07)	
Age					
<75 yr	4.2		5.2	0.80 (0.64–1.00)	0.32
≥75 yr	7.7		10.9	0.67 (0.51–0.86)	
Sex					
Female	4.6		5.4	0.84 (0.62–1.14)	0.45
Male	5.5		7.6	0.72 (0.59–0.88)	
Race					
Black	4.3		5.7	0.77 (0.55–1.06)	0.83
Nonblack	5.6		7.3	0.74 (0.61–0.90)	
Previous CVdisease					
No	4.0		5.6	0.71 (0.57–0.88)	0.39
Yes	10.0		11.8	0.83 (0.62–1.09)	
Systolic blood pressure					
≤132 mmHg	4.5		6.3	0.70 (0.51–0.95)	0.77
>132 to <145 mmHg	5.2		6.8	0.77 (0.57–1.03)	
≥145 mmHg	5.9		7.3	0.83 (0.63–1.09)	



20066 M

The SPRINT Research Group, NEJM 2015; 373: 2103-2116

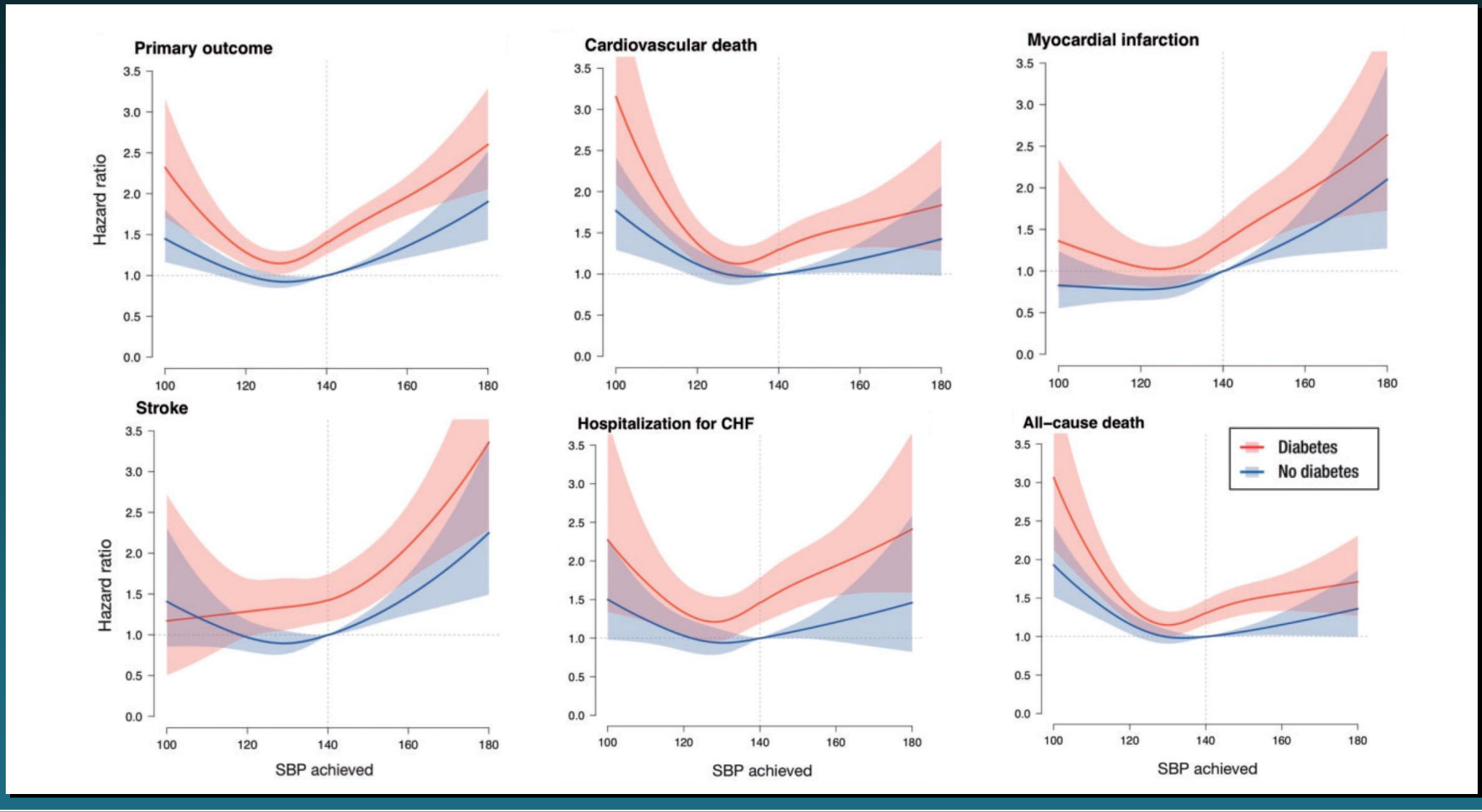
Relationships of Numbers of Outcomes Prevented and Numbers of Excess in Treatment Discontinuations* to the Extent of SBP Reductions



* Attributed to treatment adverse events

Thomopoulos, Parati, Zanchetti, J Hypertens 2016; 34: 1451-1463

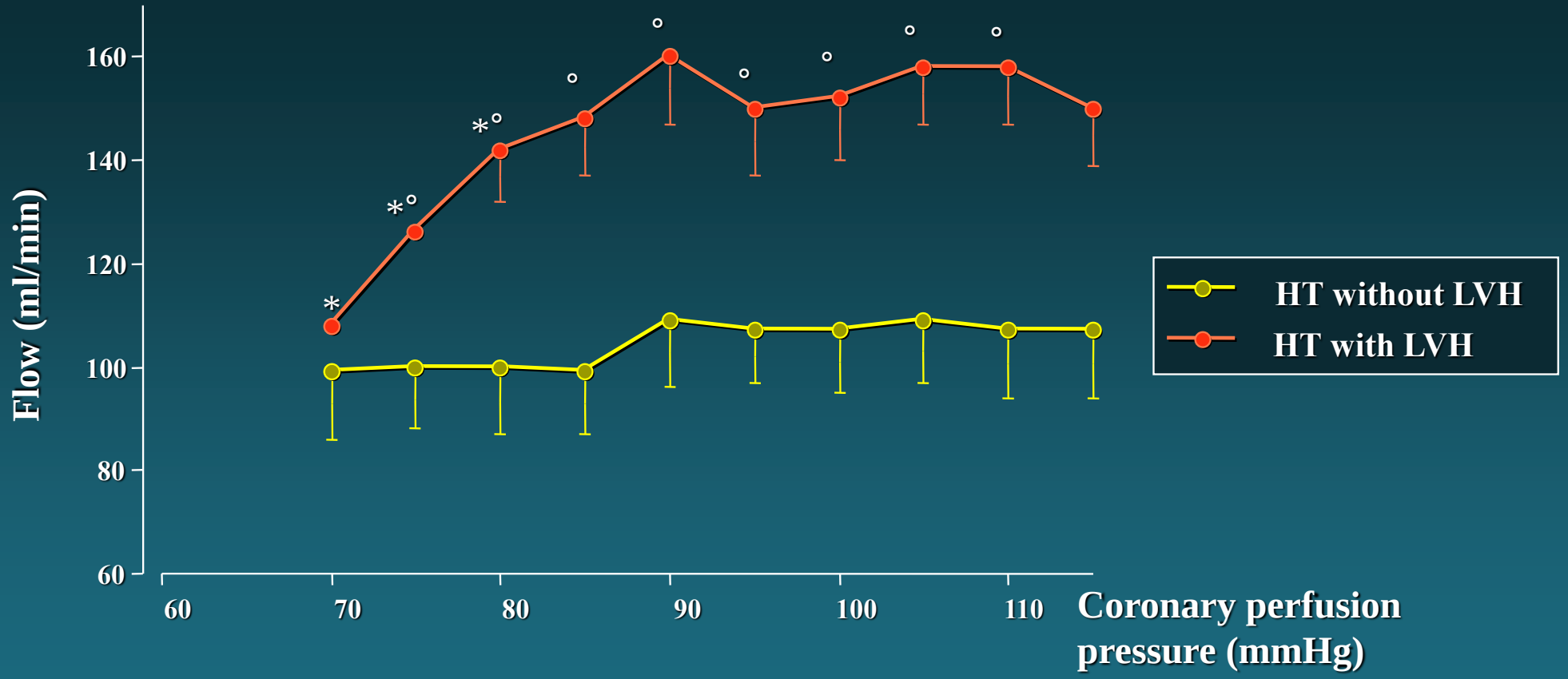
Hazard ratio according to mean achieved SBP for the adjusted hazard ratios for primary outcome, CV death, myocardial infarction, stroke, hospitalization for CHF, and all-cause death



20579 M

Böhm, Schumacher, Teo, Lonn, Mahfoud, Mann, Mancia, Redon, Schmieder, Marx, Sliwa, Weber, Williams, Yusuf, Eur Heart J 2019, doi:10.1093/eurheartj/ehz149

Stepwise Reduction of Coronary Perfusion Pressure in Hypertensives Patients Without and With LVH and Corresponding Flow in Great Cardiac Vein



* p < 0.01 vs baseline
° p < 0.01 vs HT without LVH

16482a = 12719 M mod

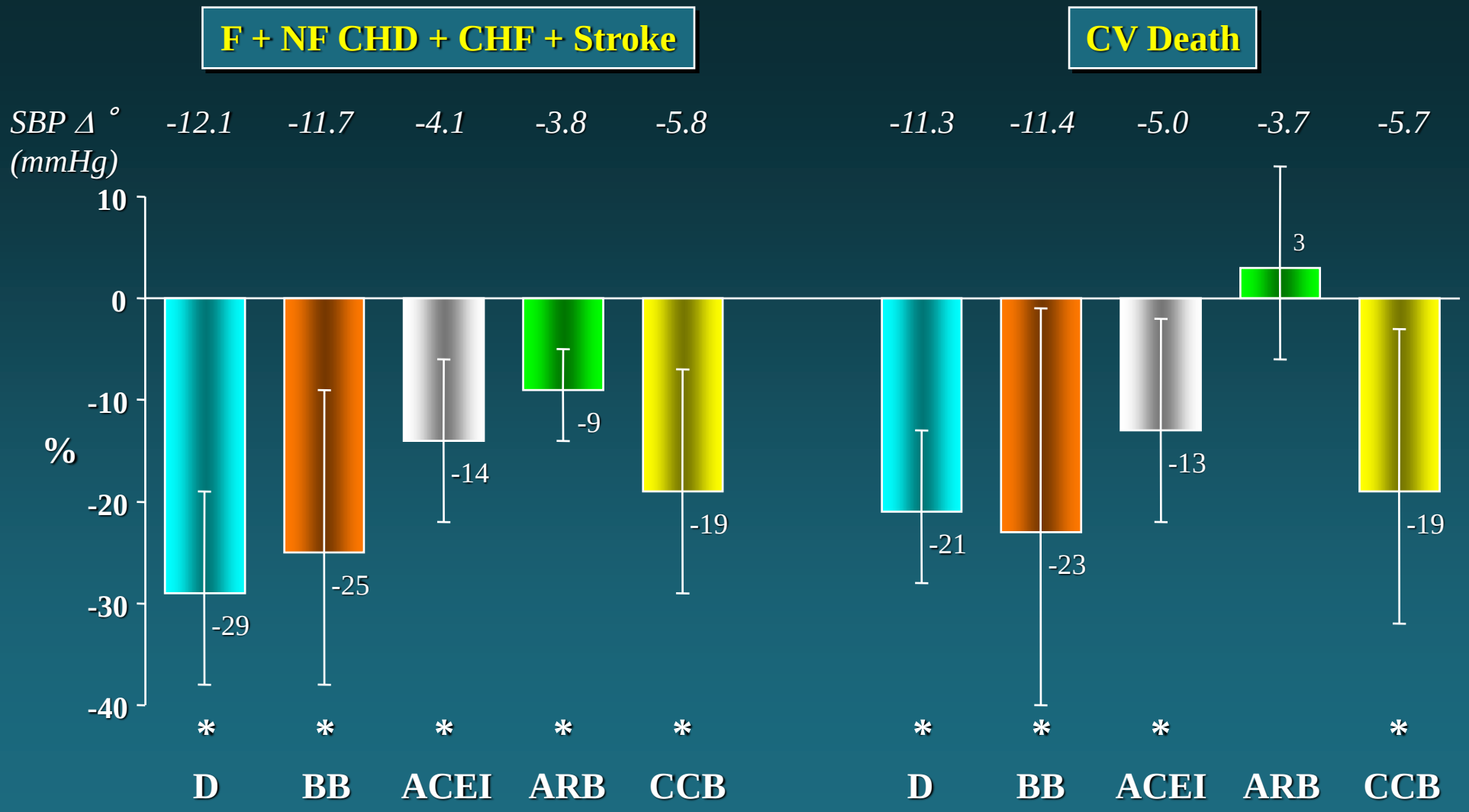
Polese A et al., Circulation 1991; 83: 845

Priorital antihypertensive drugs in US and EU GLs

- US GLs:preference to chlortalidone/EU GLs:equal status for chlortalidone, indapamide, HCTZ
- US GLs: D/ACEI/ARB/CCB
- EU GLs: D/ACEI/ARB/CCB/BB

  - Effective and similar BP reduction
  - CV protection against placebo in RCTs
  - Similar degree of overall CV protection in several comparison RCTs and meta-analyses

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



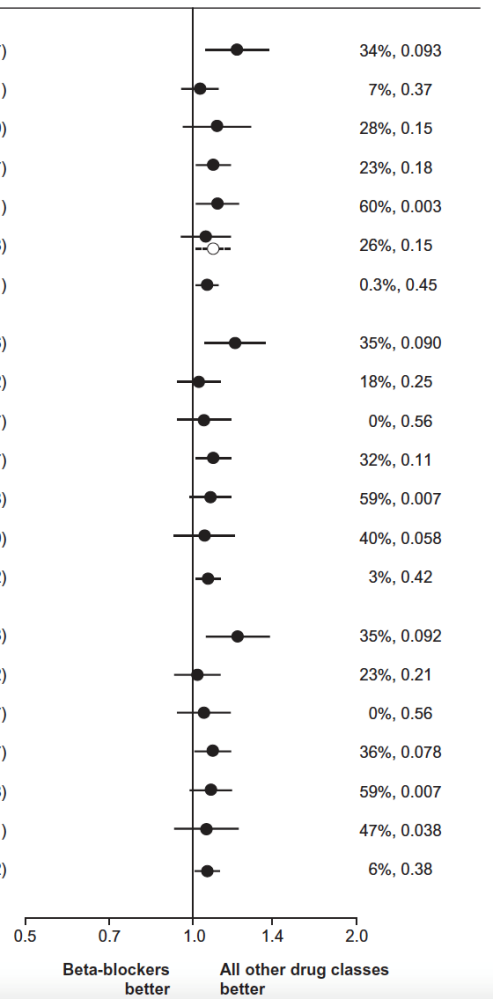
° Sign "-" means lower SBP in drug group; * Statistically significant

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

19992 M

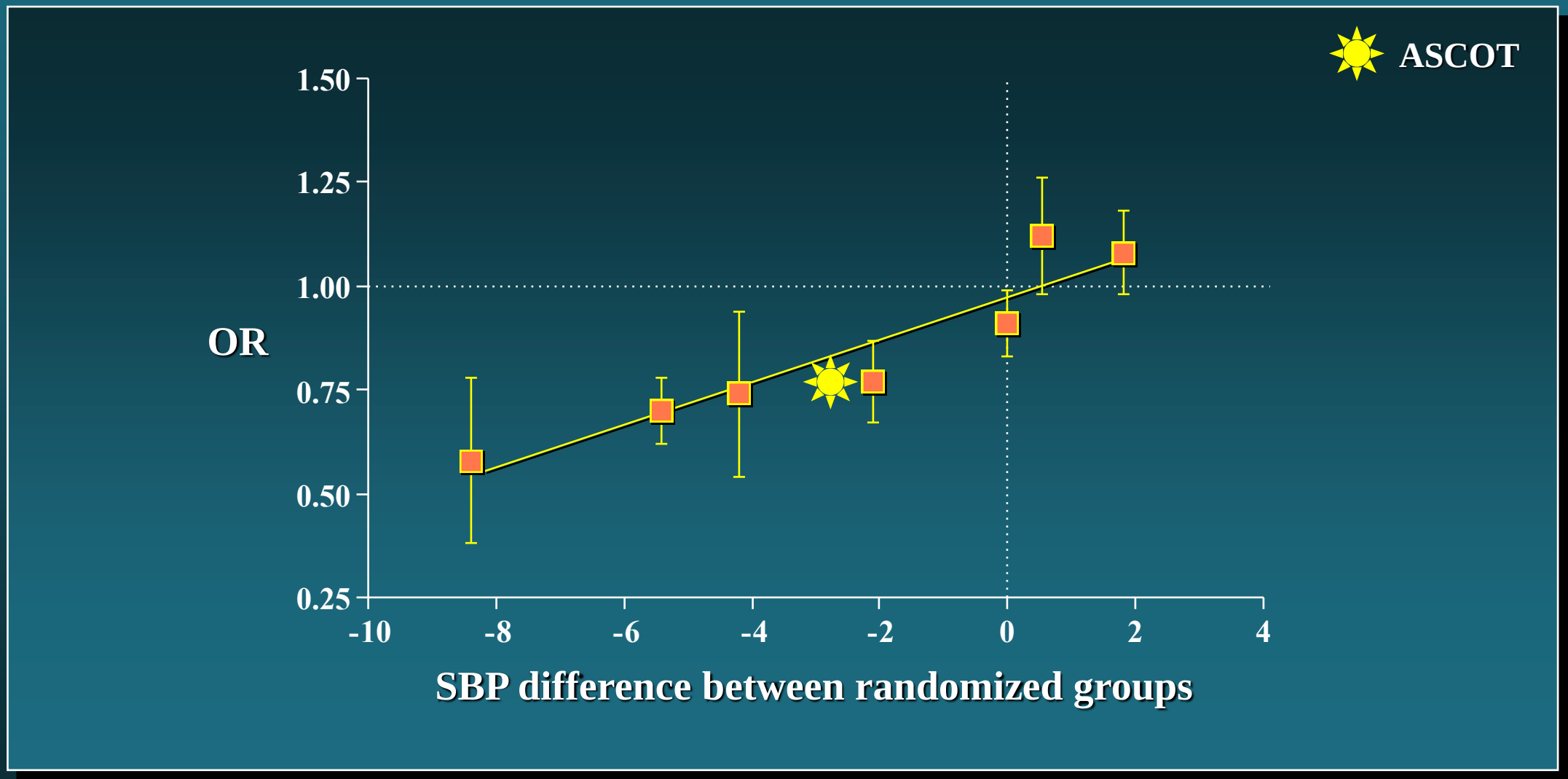
Comparisons of BP-lowering treatment based on BBs with treatments based on all other drug classes considered together

	Outcome	Trials (n)	Difference SBP/DBP (mmHg)	Events (n/patients) Beta-blockers	Events (n/patients) All other drug classes	RR (95% CI)	I-squared, *P*-value
(a) All selected studies	Stroke	16	0.79/0.26	1212/41873	1008/43146	1.20 (1.06-1.37)	34%, 0.093
	CHD	19	0.78/0.27	1597/42243	1564/43522	1.03 (0.95-1.11)	7%, 0.37
Baseline BP: 158/93 mmHg	HF	15	0.38/0.16	696/35393	654/36719	1.11 (0.96-1.29)	28%, 0.15
	Stroke + CHD	18	0.67/0.35	2990/46379	3082/55216	1.09 (1.02-1.17)	23%, 0.18
	Stroke + CHD + HF	13	0.84/0.28	3364/40095	3101/41295	1.10 (1.01-1.21)	60%, 0.003
	CV Death	18	0.80/0.26	1386/41604	1288/41715	1.06 (0.95-1.18)	26%, 0.15
	All-cause Death	22	0.75/0.25	2872/42890	2763/44116	1.06 (1.01-1.11)	0.3%, 0.45
(b) Exclusion of acute myocardial infarction and HF studies	Stroke	15	0.80/0.27	1208/41328	1007/42601	1.20 (1.05-1.36)	35%, 0.090
	CHD	16	0.80/0.27	1587/41554	1554/42833	1.03 (0.94-1.12)	18%, 0.25
	HF	9	0.40/0.17	619/33985	605/35312	1.05 (0.94-1.17)	0%, 0.56
Baseline BP: 159/93 mmHg	Stroke + CHD	16	0.67/0.34	2980/45774	3073/54611	1.09 (1.02-1.17)	32%, 0.11
	Stroke + CHD + HF	11	0.84/0.28	3330/39490	3086/40690	1.09 (0.99-1.18)	59%, 0.007
	CV Death	4	0.84/0.27	1343/40340	1247/40452	1.05 (0.93-1.19)	40%, 0.058
	All-cause Death	16	0.79/0.26	2818/41482	2709/42709	1.06 (1.01-1.12)	3%, 0.42
(c) Only hypertension studies	Stroke	14	0.81/0.27	1196/40922	992/42198	1.21 (1.07-1.38)	35%, 0.092
	CHD	14	0.81/0.27	1544/40922	1519/42198	1.02 (0.93-1.12)	23%, 0.21
Baseline BP: 160/94 mmHg	HF	9	0.41/0.17	619/33985	605/35312	1.05 (0.94-1.17)	0%, 0.56
	Stroke + CHD	15	0.68/0.34	2940/45368	3040/54208	1.09 (1.01-1.17)	36%, 0.078
	Stroke + CHD + HF	11	0.84/0.28	3330/39490	3086/40690	1.09 (0.99-1.18)	59%, 0.007
	CV Death	12	0.85/0.27	1321/39708	1222/39817	1.06 (0.93-1.21)	47%, 0.038
	All-cause Death	14	0.80/0.27	2793/40850	2678/42074	1.06 (1.01-1.12)	6%, 0.38



Thomopoulos, Bazoukis, Tsioufis, Mancia, J Hypertens 2020; 38: 1669-1681

Reduction of stroke risk in CCB compared to BB group (ASCOT) vs the metaregressio on the relationship between T-induced fall in BP and stroke

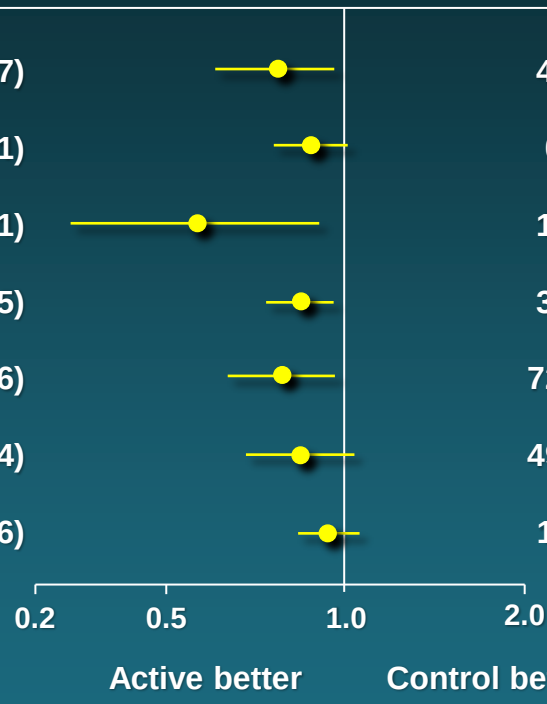


12639 M

Mancia & Zanchetti , J Hypertens 2008; 26: 164/ BP Coll Group Trialists, Lancet 2003, 362,1527

Relative risk reduction of various outcomes in BP-lowering trials on BB treatment versus placebo, no treatment or less and no BB-based treatment
Only hypertension studies (Baseline BP 163.0/94.3mmHg)

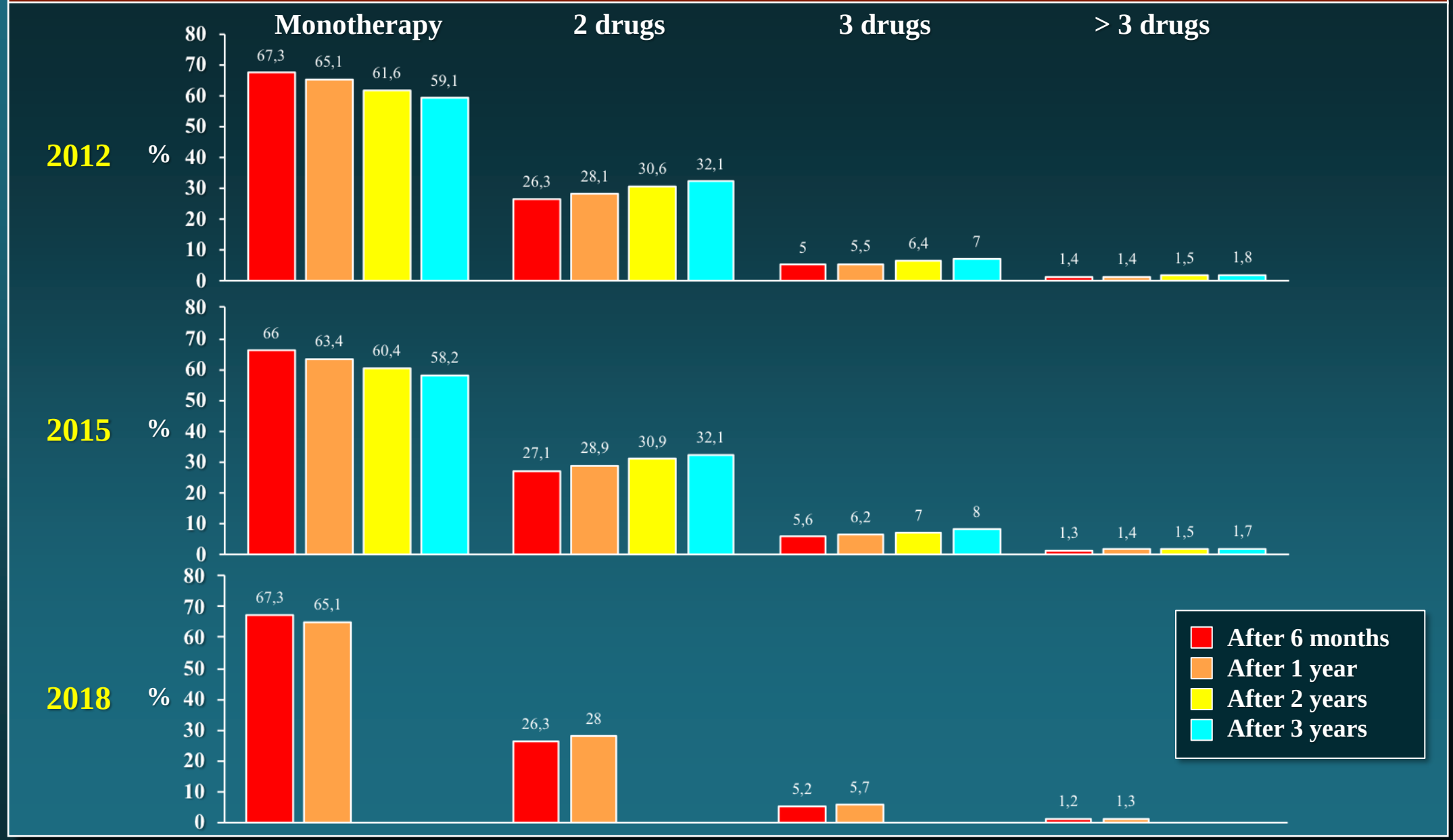
Outcome	Trials (n)	Difference SBP/DBP (mmHg)	Events (n/patients) Active	Events (n/patients) Control	RR (95% CI)	RR (95% CI)	I-squared, P-value
Stroke	5	-10.5/-7.0	216/6654	394/12070	0.77 (0.61-0.97)		45%, 0.12
CHD	5	-10.5/-7.0	293/6654	538/12070	0.88 (0.77-1.01)		0%, 0.47
HF	2	-14.8/-8.7	31/ 777	60/ 855	0.57 (0.35-0.91)		16%, 0.28
Stroke + CHD	5	-10.5/-7.0	509/6654	932/12070	0.84 (0.74-0.95)		33%, 0.20
Stroke + CHD + HF	4	-10.7/-7.1	446/6282	903/11722	0.78 (0.64-0.96)		72%, 0.014
CV Death	5	-10.5/-7.0	258/6654	466/12070	0.84 (0.68-1.04)		49%, 0.097
All-cause Death	5	-10.5/-7.0	457/6654	780/12070	0.95 (0.84-1.06)		11%, 0.34



21042 M

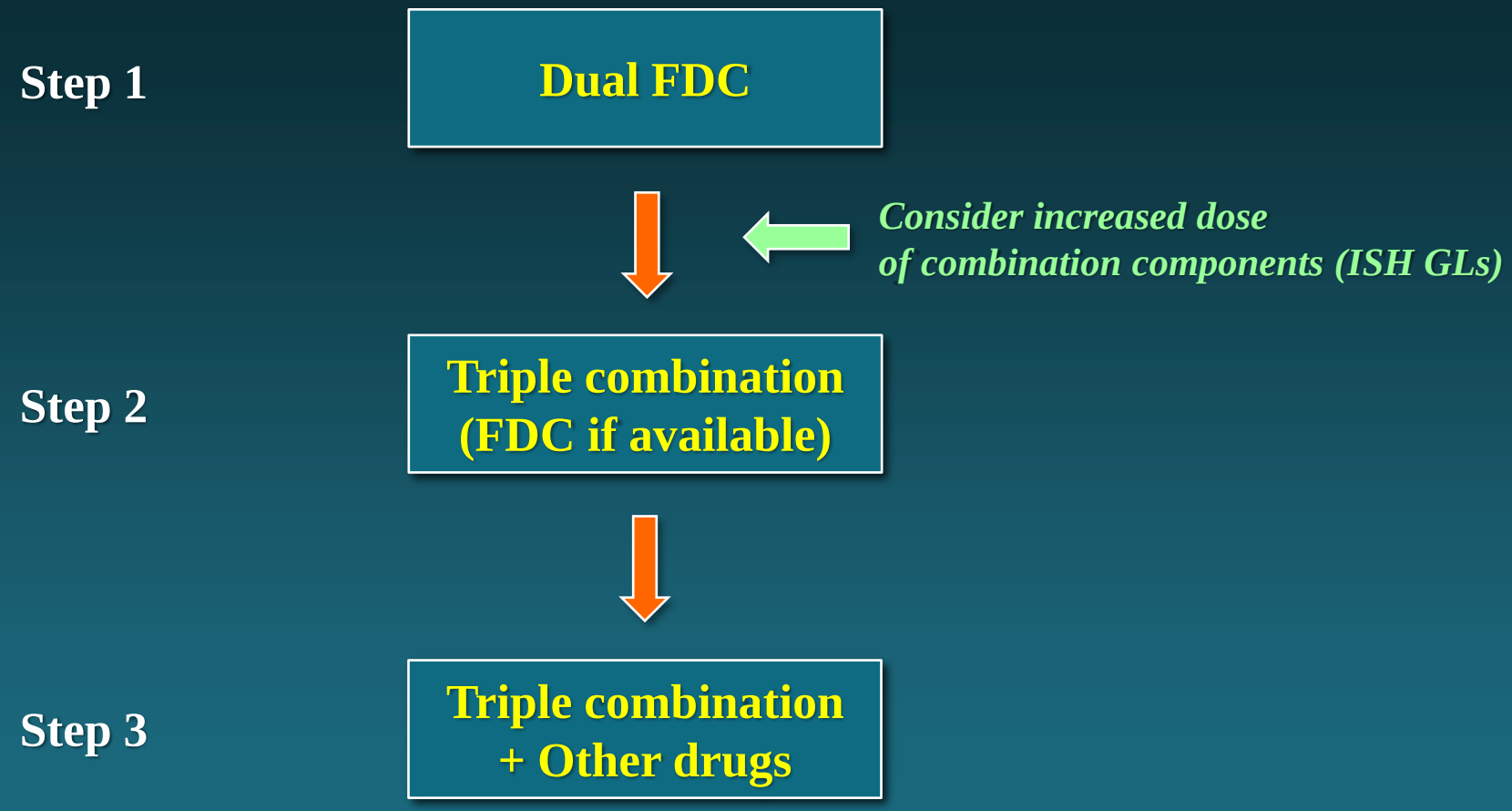
Thomopoulos, Bazoukis, Tsioufis, Mancia. J Hypertens 2020; 38: 1669-1681

Antihypertensive monotherapy and combination treatment over 3 years in Lombardy data-base



Rea, Corrao, Mancia, unpublished

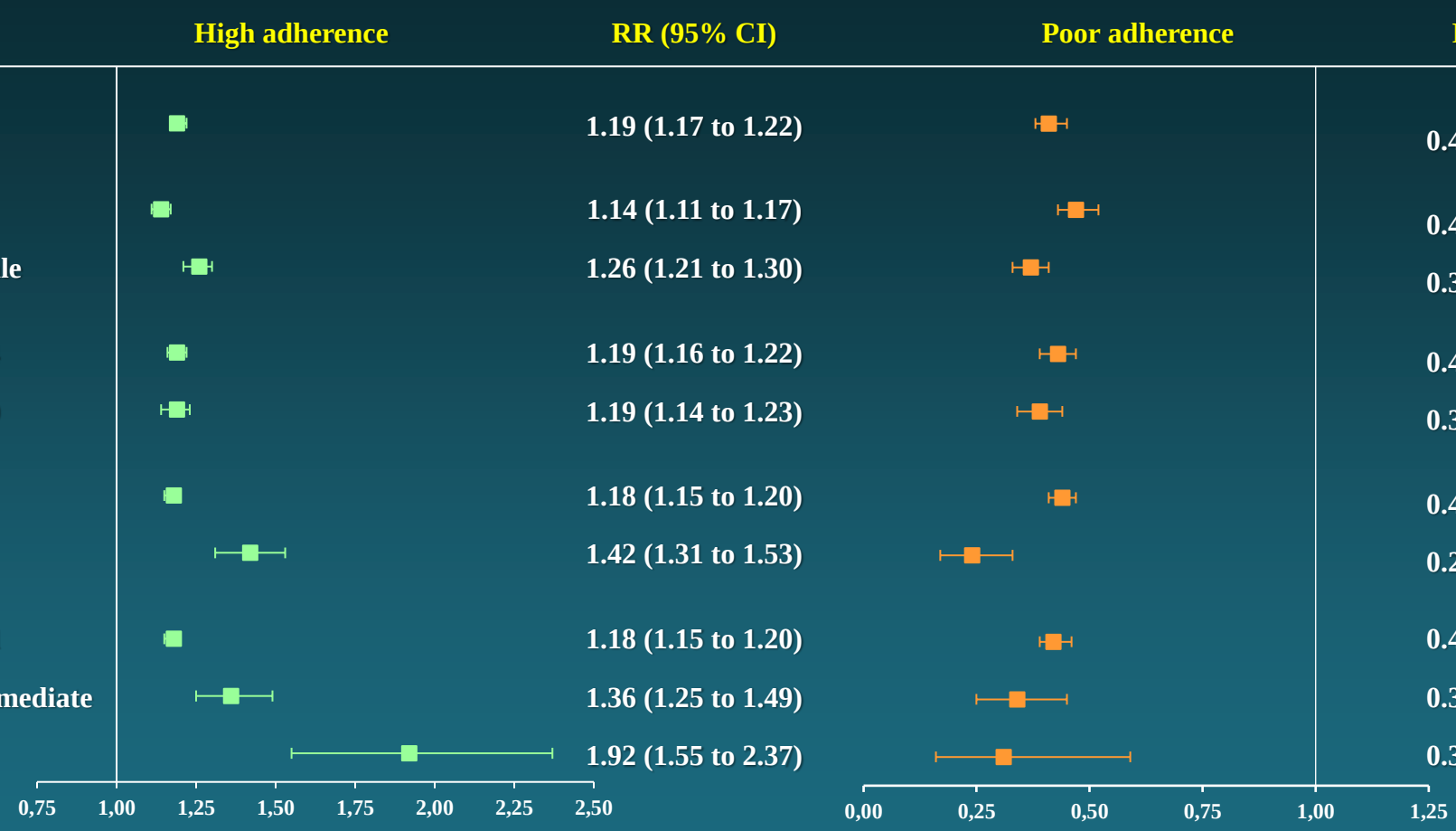
Core drug treatment strategy for hypertension



20958 M

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

Adjusted odds of achieving high* or avoiding low ** adherence to treatment in patients starting treatment with antihypertensive monotherapy (n=53702) vs dual FDC (n=9746) in Lombardy

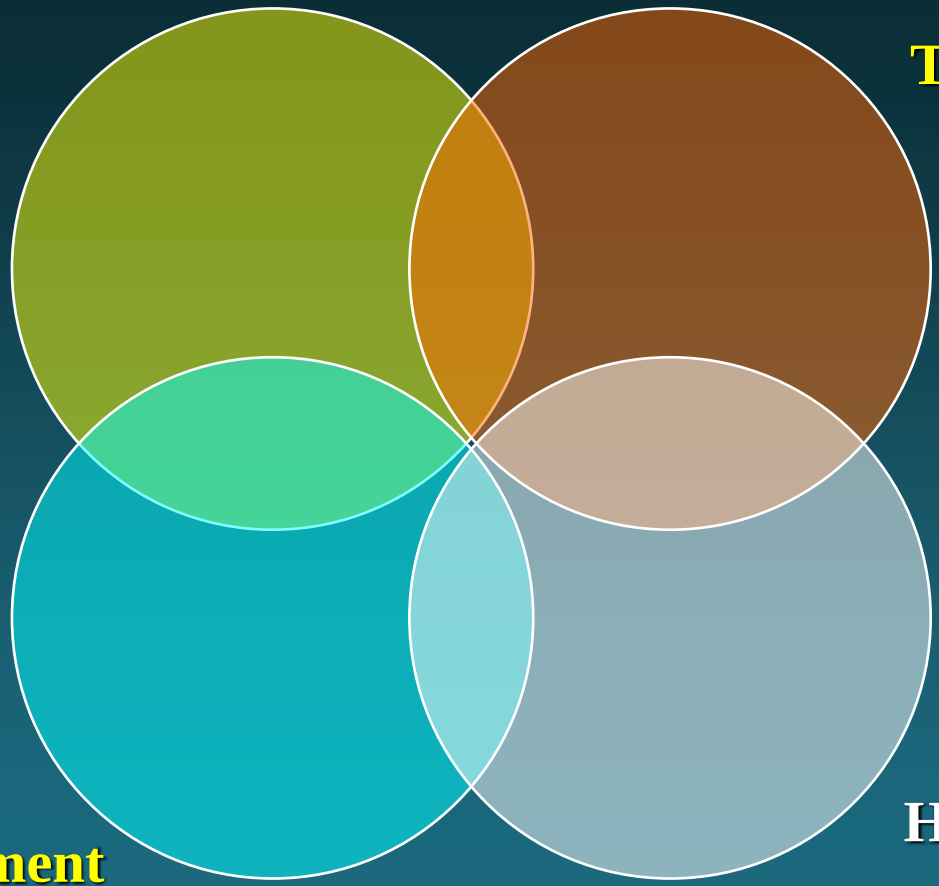


* high (>75% of the 1 year prescription time)
** low (<25% of the 1 year prescription time)

20957 M

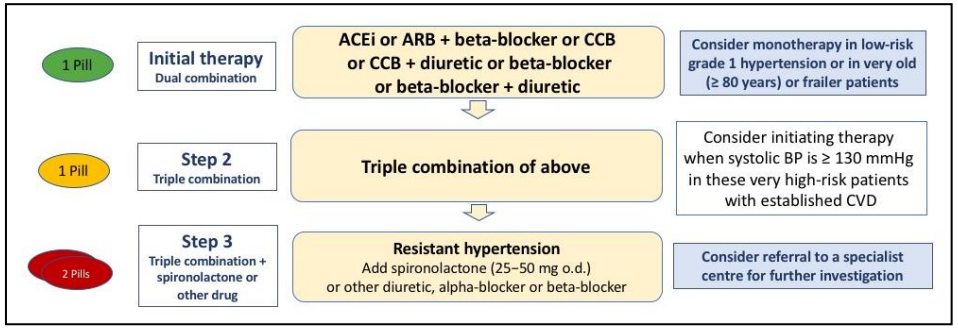
Rea, Corrao, Mancia et al, Amer J Hypertens 2021

Factors Involved in Poor Control of BP

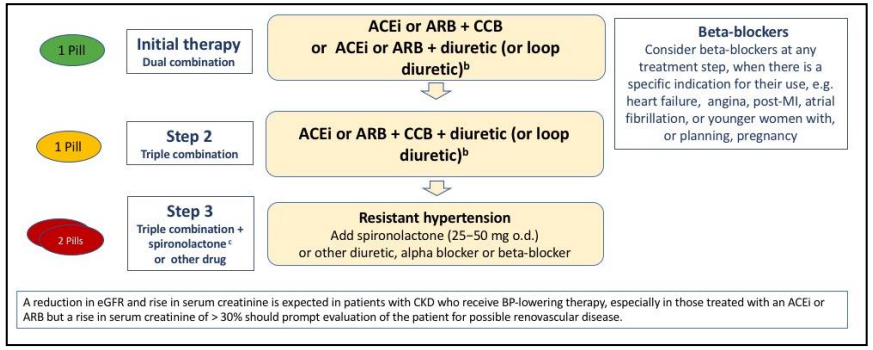


Drug-treatment strategies

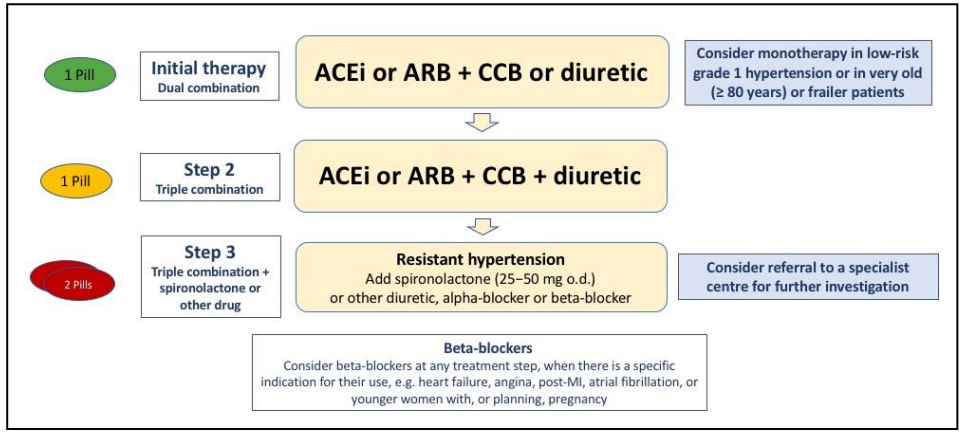
Hypertension and CAD



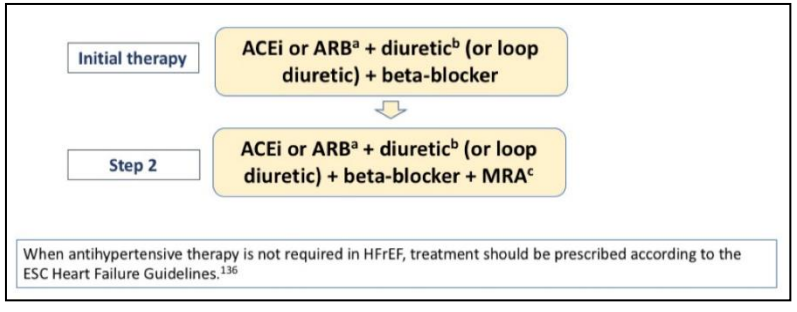
Hypertension and CKD



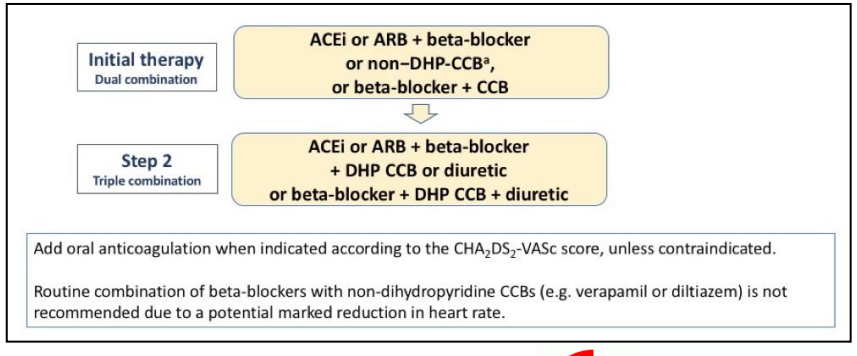
Core drug-treatment strategy for uncomplicated hypertension



Hypertension and HRrEF



Hypertension and AF



ESC European Society of Cardiology

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

ESH European Society of Hypertension

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

Drug choice in GLs/Restricted or Expanded?

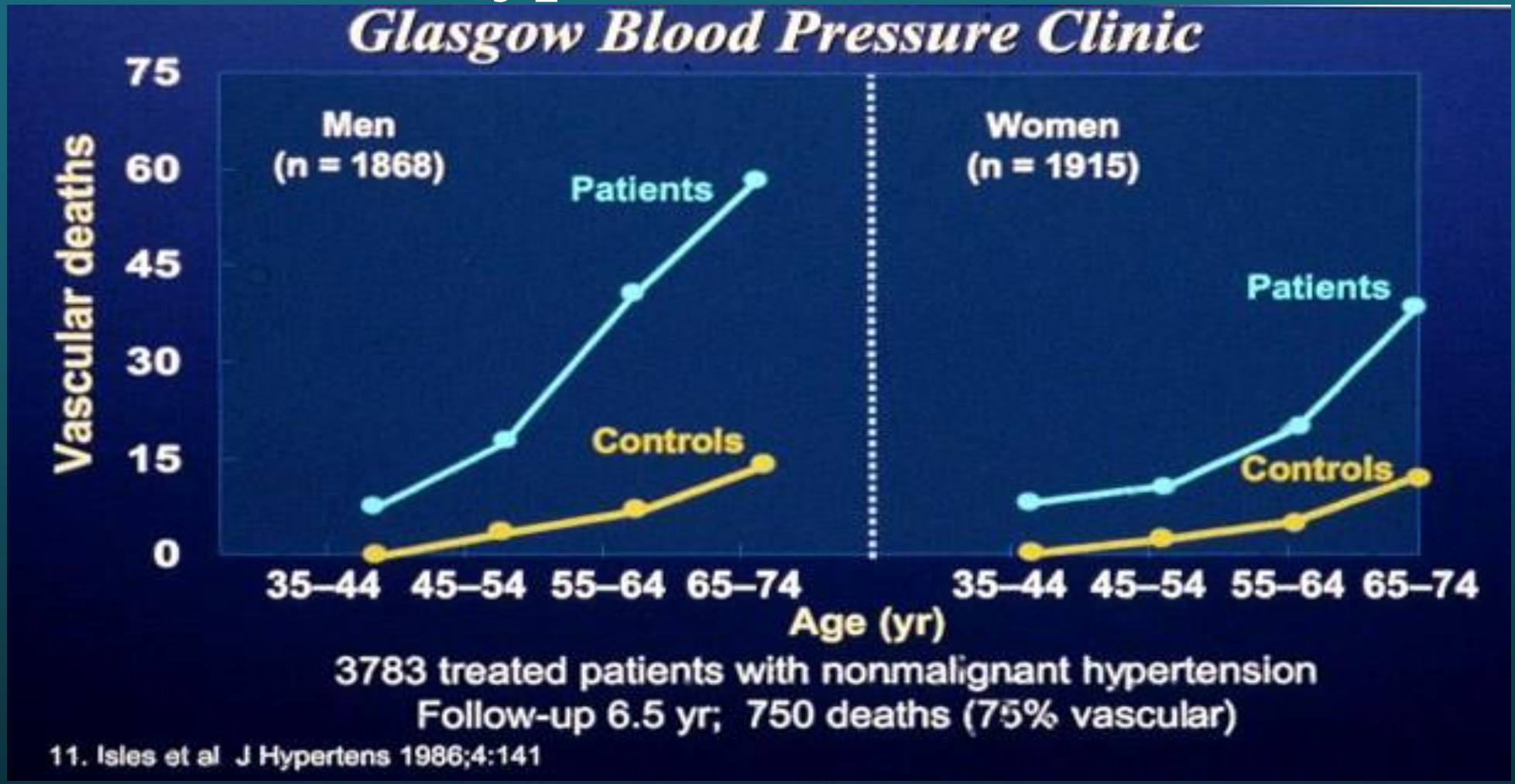
- Patients responsive to one drug class are frequently different from those responsive to another drug class
- Multiple drug options extend number of responders&facilitate drug replacement (in case of side effects)
- Restricting the number of drug options is against personalized/precision medicine.

Frequency of Office BP re-measurements According to BP values in GLs

	ACC/AHA	ESC/ESH
BP <120/80mmHg	1 year	5 years
BP 120-129/80-84mmHg*	3-6 months	3 years
BP 130/139/85-89mmHg**	-	1 year

- *-80 in ACC/AHA Gls
- ** grade 1 hypertension for ACC/AHA Gls

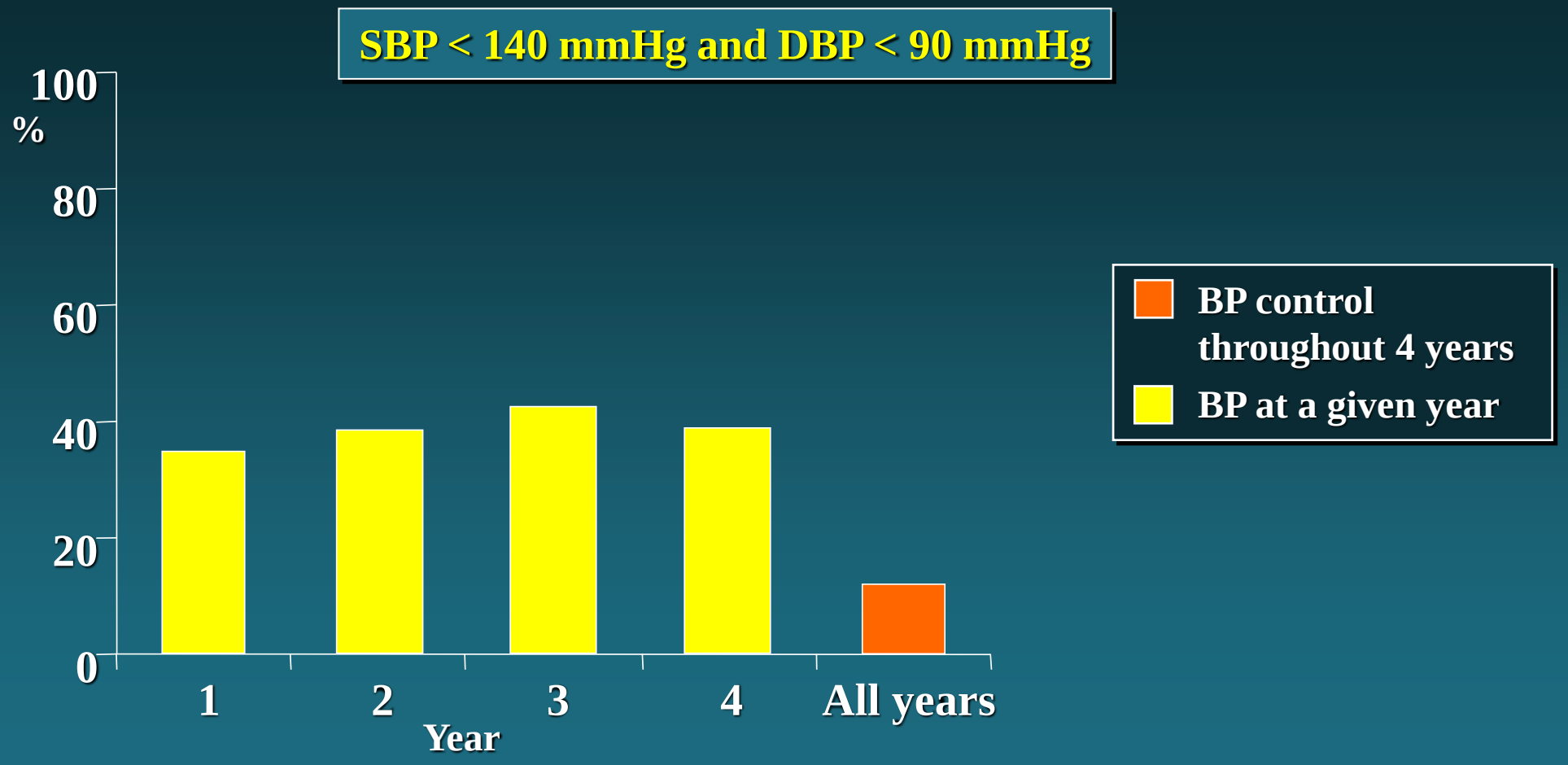
Persisting Cardiovascular Risk in Treated Hypertensive Patients



Reducing residual risk in treated HTs/Options

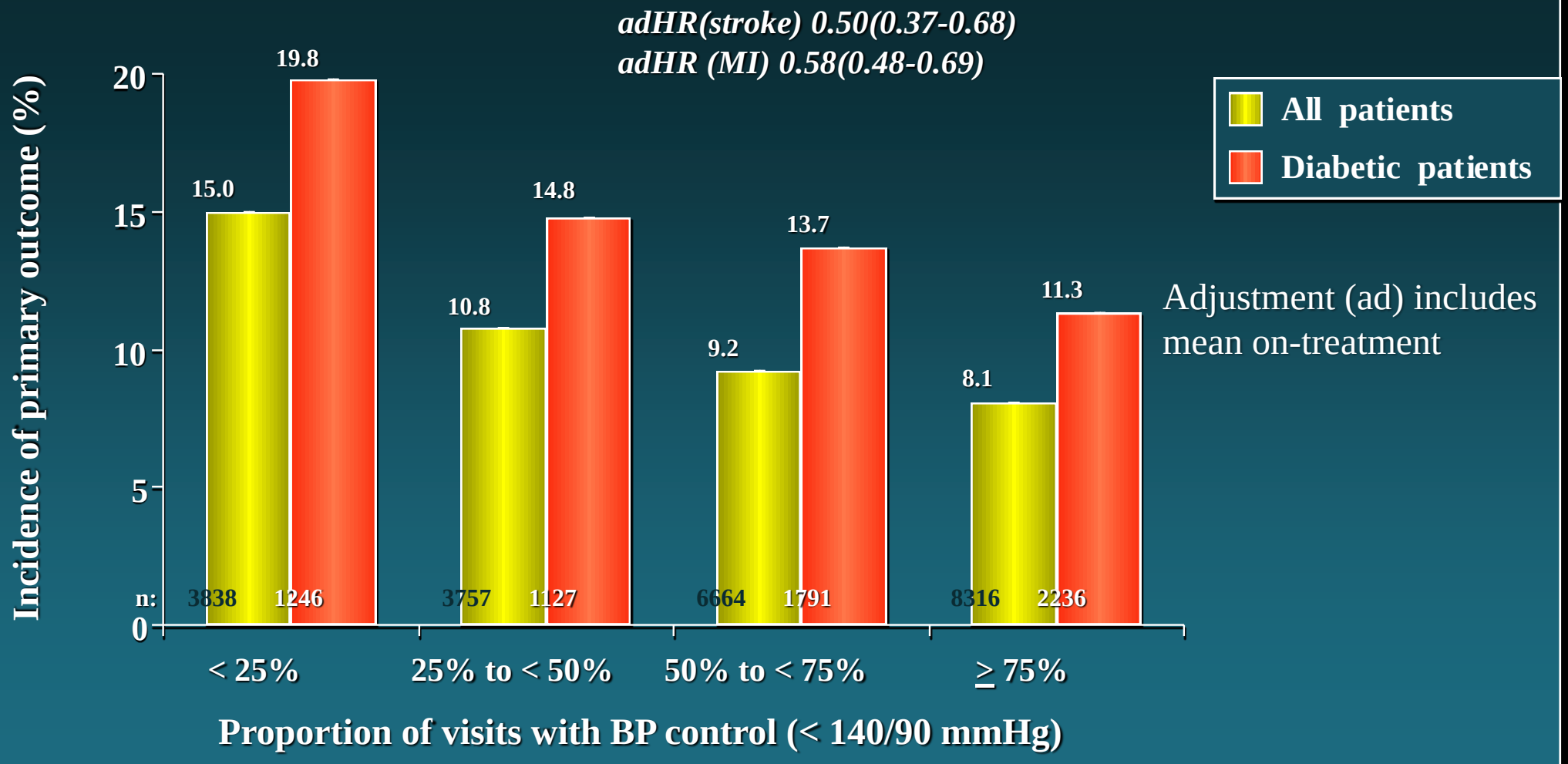
- Is there a risk fraction unmodifiable?
- Associated risk factor control
- Individualized BP targets (higher in some/lower in other pts)
- Out-of-office BP control
- Short/Long term BP variability reduction
- Earlier treatment initiation (when risk still low)

Rate of Clinic BP Normalization at Each Year and Throughout the 4 Years of Treatment in ELSA



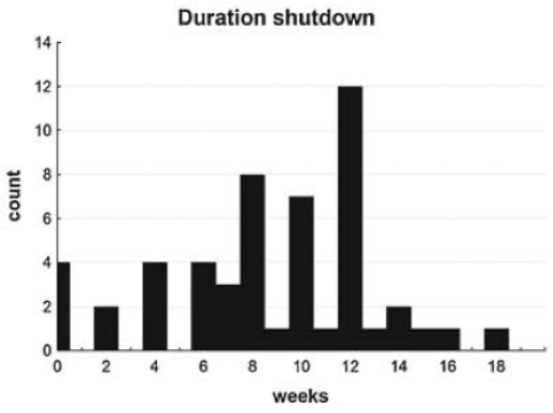
Mancia et al., J Hypertens 2007; 25: 1087-1094

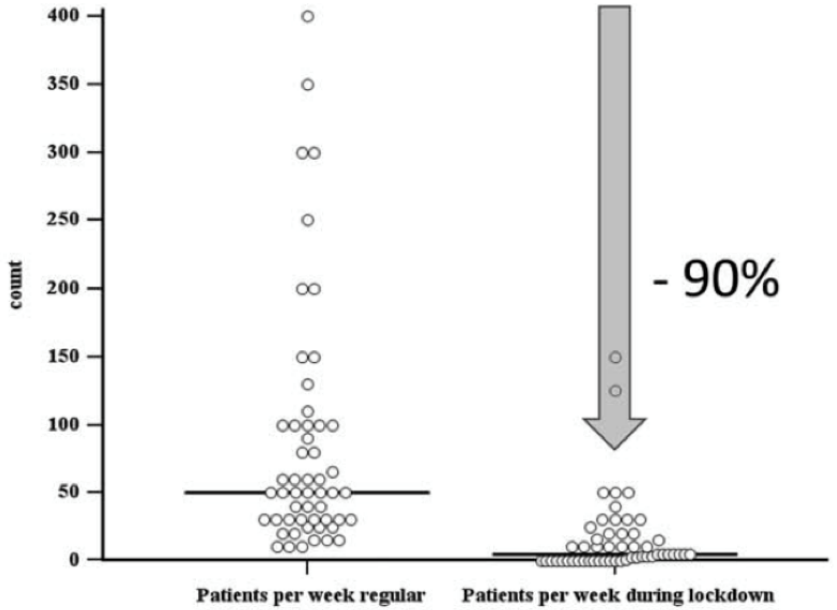
INVEST: BP Control and Incidence and risk of Primary Outcome in All Patients and in Diabetic Patients

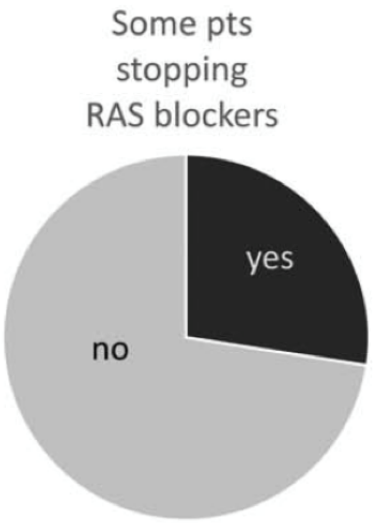


Mancia et al., Hypertension 2007; 50: 299

Summary of the effects of corona-virus disease 2019 and the associated shutdown of routine healthcare services for hypertensive patients







21131 M

ESH Covid-19 Task Force J Hypertens 2021, 39:190–195

Use of ARBs, ACEIs and other antihypertensive drugs in patients with Covid-19 infection (cases*)and corresponding matched controls

	Cases (N=6,272)	Controls (N=30,759)	Relative difference
Age, years - mean (SD)	68 (13)	68 (13)	MV
Women	2,303 (37%)	11,357 (37%)	MV
Drugs:			
Antihypertensive drugs	3,632 (57.9%)	15,319 (49.8%)	+14.0%
ACEIs	1,502 (23.9%)	6,569 (21.4%)	+10.5%
ARBs	1,394 (22.2%)	5,910 (19.2%)	+13.3%
CCBs	1,446 (23.1%)	5,926 (19.3%)	+13.1%
β-blockers	1,826 (29.1%)	7,123 (23.2%)	+20.5%
Diuretics	1,902 (30.4%)	7,420 (24.1%)	+20.5%
Thiazide/Thiazide-like	1,104 (17.6%)	5,074 (16.5%)	+6.4%
Loop	871 (13.9%)	2,411 (7.8%)	+43.6%
MRA	239 (3.8%)	738 (2.4%)	+37.1%
Monotherapy	1,067 (17.1%)	4,903 (15.9%)	+6.4%
Combination therapy	2,565 (40.9%)	10,416 (33.9%)	+17.3%

* MV: Matching variables

* Diagnosed from February 21 until March 11 2020

Mancia, Rea, Ludergnani, Apolone and Corrao, NEJM 2020, May 1st

Adjusted odds ratios of Covid-19 infection associated with use of BP-lowering drugs in monotherapy or combination therapy (n=6272 with Covid-19 vs 30759 controls)

BP-Lowering Drugs	Odds Ratio (95% CI)		Odds Ratio (95% CI)
BP lowering as a whole			
ACEIs	0.96 (0.87 to 1.07)	No use during 2019	1.00 (reference)
ARBs	0.95 (0.86 to 1.05)		
MRA	0.90(0.75 to 1.07)	Use only as monotherapy	1.03 (0.90 to 1.18)
CCBs	1.03(0.95 to 1.12)		
β-blockers	0.99 (0.91 to 1.08)		
Thiazides/Thiazides-like	1.03(0.91 to 1.23)	Use as combination therapy	0.99 (0.90 to 1.09)

20870 M

Mancia, Rea, Ludergnani, Apolone and Corrao,NEJM 2020, May 1st

Clinical features of patients with Covid-19 infection (cases/n=6272)) and corresponding matched controls* (n=30759)

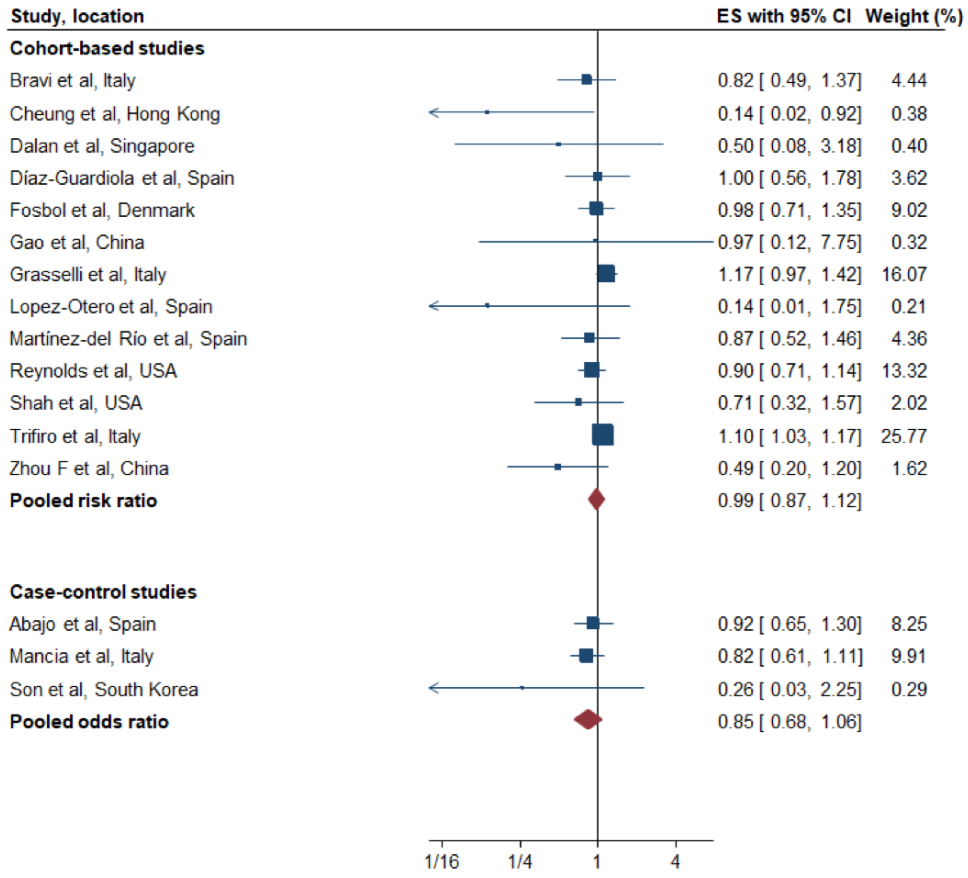
Comorbidities and associated procedures	Relative difference (Cases vs Controls)	Chronic Comorb. Score	Relative difference (Cases vs Controls)	Adjusted OR
Cardiovascular disease	+28.0%	0	-25.8%	1.00 (Reference)
Coronary artery disease	+34.6%			
Percutaneous coronary intervention	+31.3%	1	-7.2%	1.19 (1.09 to 1.31)
Heart failure	+52.1%	2	+11.4%	1.38 (1.23 to 1.54)
Respiratory diseases	+46.3%			
COPD	+53.1%	3	+25.9%	1.55 (1.34 to 1.78)
Asthma	+60.4%			
Kidney disease	+26.8%	4	+38.2%	1.57 (1.34 to 1.84)
Chronic kidney disease	+55.8%			
Dialysis	+77.6%			
Cancer	+13.3%			

* Cases diagnosed from February 21 to March 11 2020

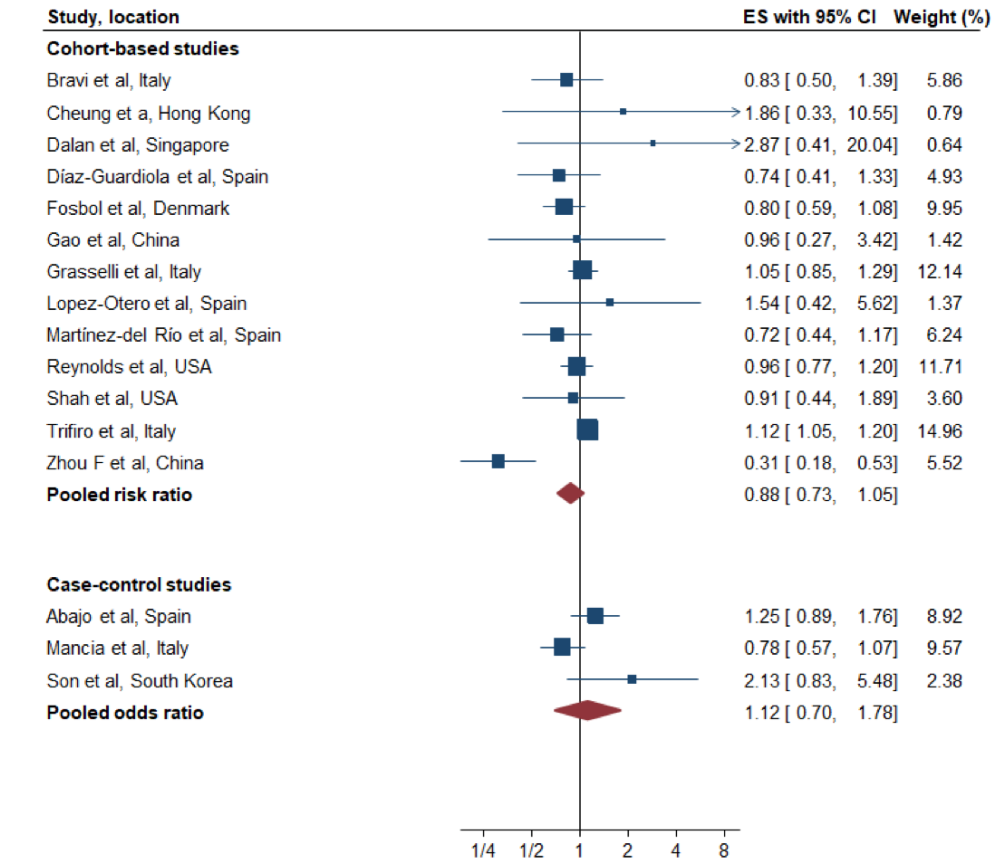
Mancia, Rea, Ludergnani, Apolone and Corrao, NEJM 2020, May 1st

Forest plot of the association between ACEI or ARB treatment and all-cause mortality/severe disease in 87951 patients hospitalized with COVID-19 infection

ACEI



ARB



21049 M

Bavishi, Whelton, Mancia, Corrao, Messerli, J Hypertens 2021,39,784

Adjusted odds ratios of Covid-19 infection associated with use of BP-lowering drugs in monotherapy or combination therapy (n=6272 with Covid-19 vs 30759 controls)

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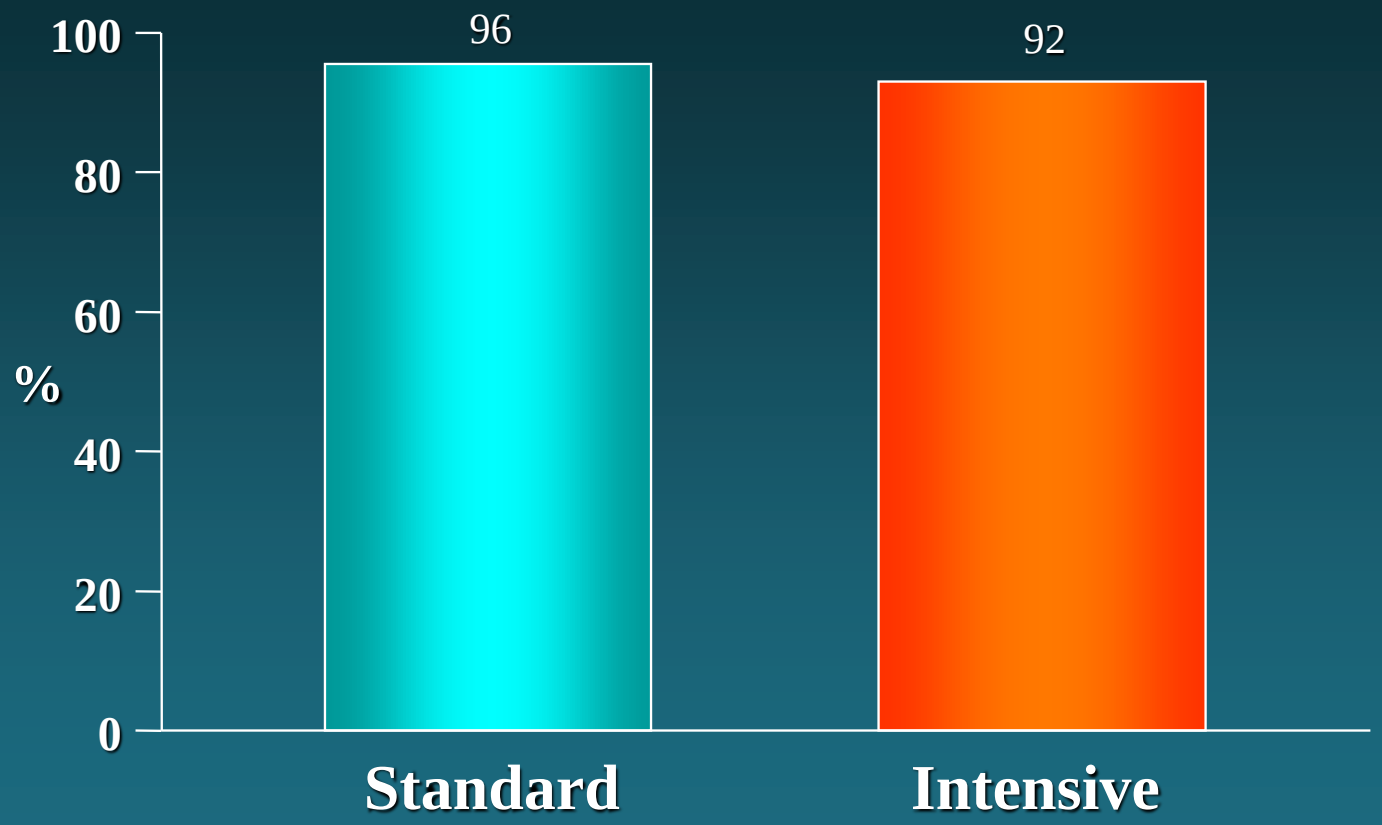
ARBs	0.95 (0.86 to 1.05)		
MRA	0.90(0.75 to 1.07)	Use only as monotherapy	1.03 (0.90 to 1.18)
CCBs	1.03(0.95 to 1.12)		
β-blockers	0.99 (0.91 to 1.08)		
Thiazides/Thiazides-like	1.03(0.91 to 1.23)	Use as combination therapy	0.99 (0.90 to 1.09)

Mancia, Rea, Ludergnani, Apolone and Corrao,NEJM 2020, May 1st

In SPRINT pts were at high CV risk and initial BP was in the high normal range but virtually all of them were treated at baseline



20159 M

The SPRINT Research Group, NEJM 2015,373,2103

Sensitivity to detect treatment-induced changes, reproducibility and operator independence, time to changes, and prognostic value of changes provided by markers of HMOD

Marker of HMOD	Sensitivity to changes	Reproducibility and operator independence	Time to changes	Prognostic value of the change
LVH by ECG	Low	High	Moderate (> 6 months)	Yes
LVH by echocardiogram	Moderate	Moderate	Moderate (> 6 months)	Yes
LVH by CMR	High	High	Moderate (> 6 months)	No data
eGFR	Moderate	High	Very slow (years)	Yes
Urinary albumin excretion	High	Moderate	Fast (weeks to months)	Moderate
Carotid IMT	Very low	Low	Slow (> 12 months)	No
PWV	High	Low	Fast (weeks to months)	Limited data
Ankle–brachial index	Low	Moderate	Slow (> 12 months)	Moderate

Office BP treatment target ranges

Age group	Office SBP treatment target ranges (mmHg)					Diastolic treatment target range (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke/TIA	
18–65 years	**Target to 130** *or lower if tolerated* Not < 120	**Target to 130** *or lower if tolerated* Not < 120	**Target to < 140 to 130** *if tolerated*	**Target to 130** *or lower if tolerated* Not < 120	**Target to 130** *or lower if tolerated* Not < 120	< 80 to 70
65–79 years	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	< 80 to 70
≥ 80 years	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	**Target to < 140 to 130** *if tolerated*	< 80 to 70
Diastolic treatment target range(mmHg)	< 80 to 70	< 80 to 70	< 80 to 70	< 80 to 70	< 80 to 70	

ESC European Society of Cardiology

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

European Society of Hypertension

How to explain the threshold and target BP gap in EU GLs?

- In US GLs Threshold/Target BP for drug treatment almost entirely coincide: >- 130/80 VS <130/80mmHg
- In EU GLs Threshold higher in most cases than Target BP: >- 140/90 vs <140/80 or <130/80mmHg

How to explain the threshold and target BP gap in EU GLs?

- In US GLs Threshold/Target BP for drug treatment almost entirely coincide: >- 130/80 VS <130/80mmHg
- In EU GLs Threshold higher in most cases than Target BP: >- 140/90 vs <140/80 or <130/80mmHg
- In EU GLs threshold BP values strictly based on recruitment BP criteria in untreated pts
- In US GLs probable use of baseline BP data <140/90mmHg even if pts were already under treatment

Preferred treatment strategies in US and EU GLs

- Combination treatment in most pts (both)
- Initial dual combination in most pts (both)
- Preferred triple therapy and additional drugs in RH similar
- In EU GLs more emphasis on

  -SPC

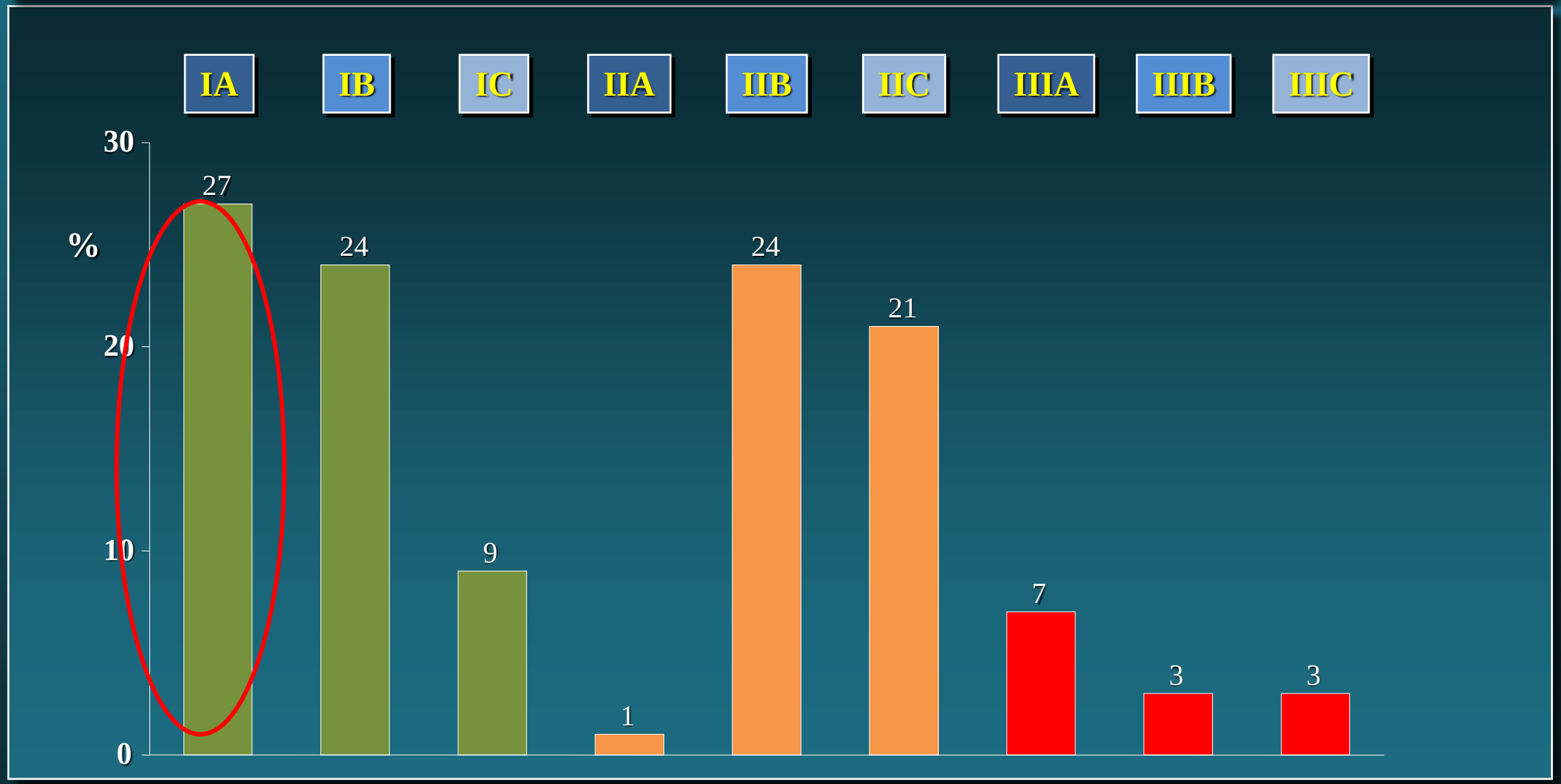
  -RAS blocker with CCB or D (uncomplicated HT)

  -Other combinations mentioned for specific conditions

Differences between ACC/AHA guidelines

- Classification of BP values
- Use of out-of-office BP
- Assessment of asymptomatic organ damage
- BP threshold for drug treatment
- BP target for drug treatment
- Major drug classes (first choice)
- Preferred treatment strategies
- Follow-up

Distribution of Combined Class / Level of Evidence in ESH/ESC Guidelines



Towsend &Mancia , HYPERTENSION,Bakris &Sorrentino (eds),Elsevier, 2018:459-468

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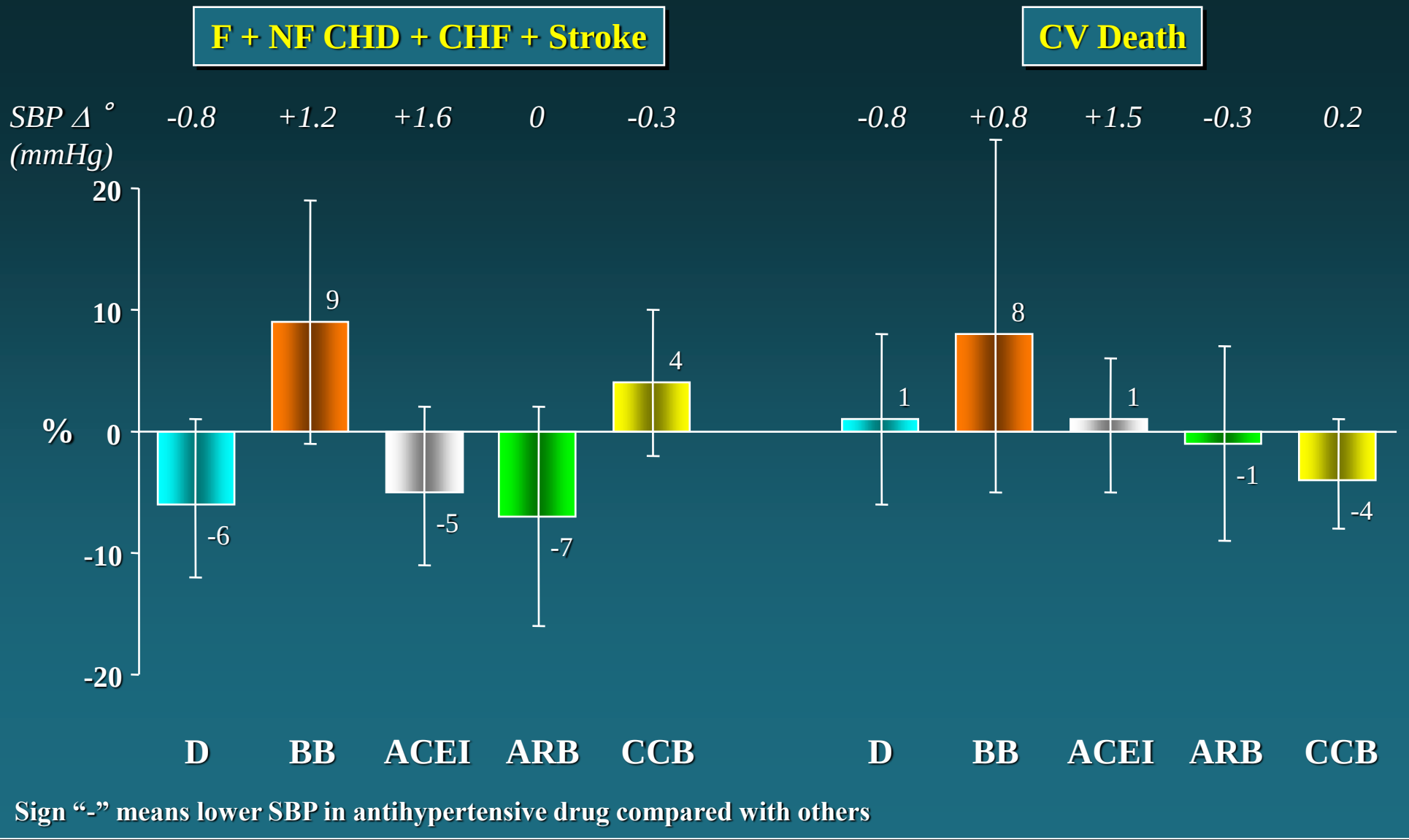
BBs are the Preferred Drugs in a large number of conditions

- Previous MI
- Angina pectoris
- Supraventricular tachyarrhythmias
  - Tachycardia
  - Permanent AF
  - Recurrent AF
- Ventricular arrhythmias
- Glaucoma
- Pregnancy
- Congestive heart failure
- Acute coronary syndrome
- Thyrotoxicosis
- Hyperkinetic syndrome
- Migraine
- Essential tremor
- Perioperative hypertension
- Excessive pressor response to exercise (and stress)
- Orthostatic hypertension
- Aortic aneurysm
- After CABG

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

19993 M

Office BP Target(mmHg) for treatment in GLs

- **European GLs*:**

  - < 140/80 (<130/80 only if treatment well tolerated)

  - Older pts/CKD <140/80 & never <130/70

- **ISH GLs*: <130/80 but <140/90 acceptable**
- **ACC/AHA GLs:< 130/80 in virtually all pts**
- **European GLs: Never <120/70(J curve)**

*** target individualized in frail pts**

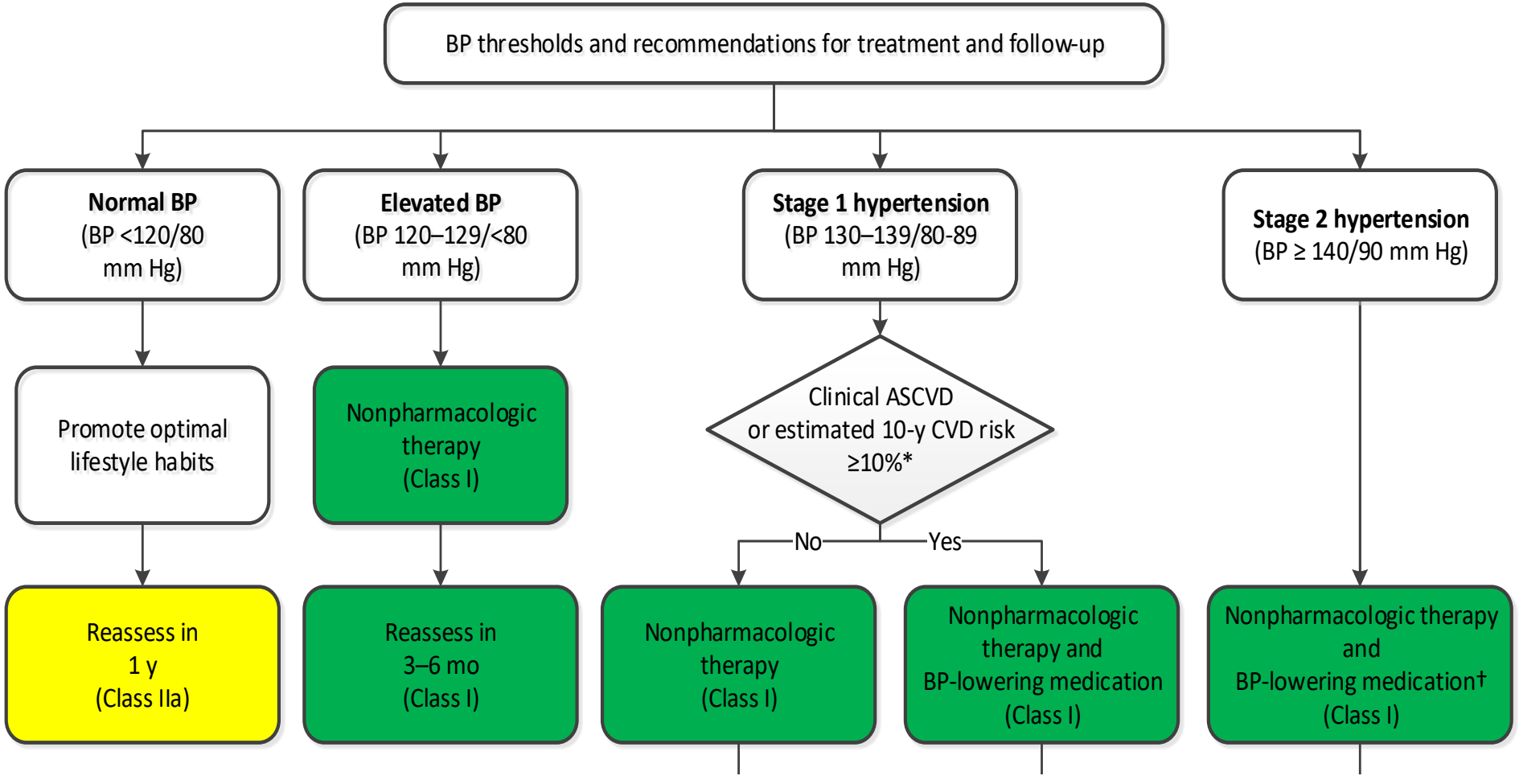
Standardized effects of 10mmHg SBP fall by beta-blockers vs other antihypertensive drugs (123 trials/n=613815)

OUTCOME	RISK (%)
CV events	+17*
Coronary disease	+3 (ns)
Heart Failure	+4 (ns)
Stroke	+24*
All Cause Mortality	+6*

* Statistically significant

Ettehad et al, Lancet,2015,387,957

Blood Pressure (BP) Thresholds and Recommendations for Treatment and Follow-Up (continued on next slide)



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BP claassification/2017 ACC-AHA GLs modifications

- BP >- 140/90mmHg (grade 2-3 HT): grade 2 HT (grade 3 eliminated)

  UNNECESSARY

- BP 120-129/80-84mmHg (normal): now «elevated»

  PARADOXICAL/POTENTIALLY HARMFUL

- BP 130-139/85-89mmHg(high normal): now «grade 1 HT»

  NEGATIVE BUT ALSO POSITIVE ASPECTS

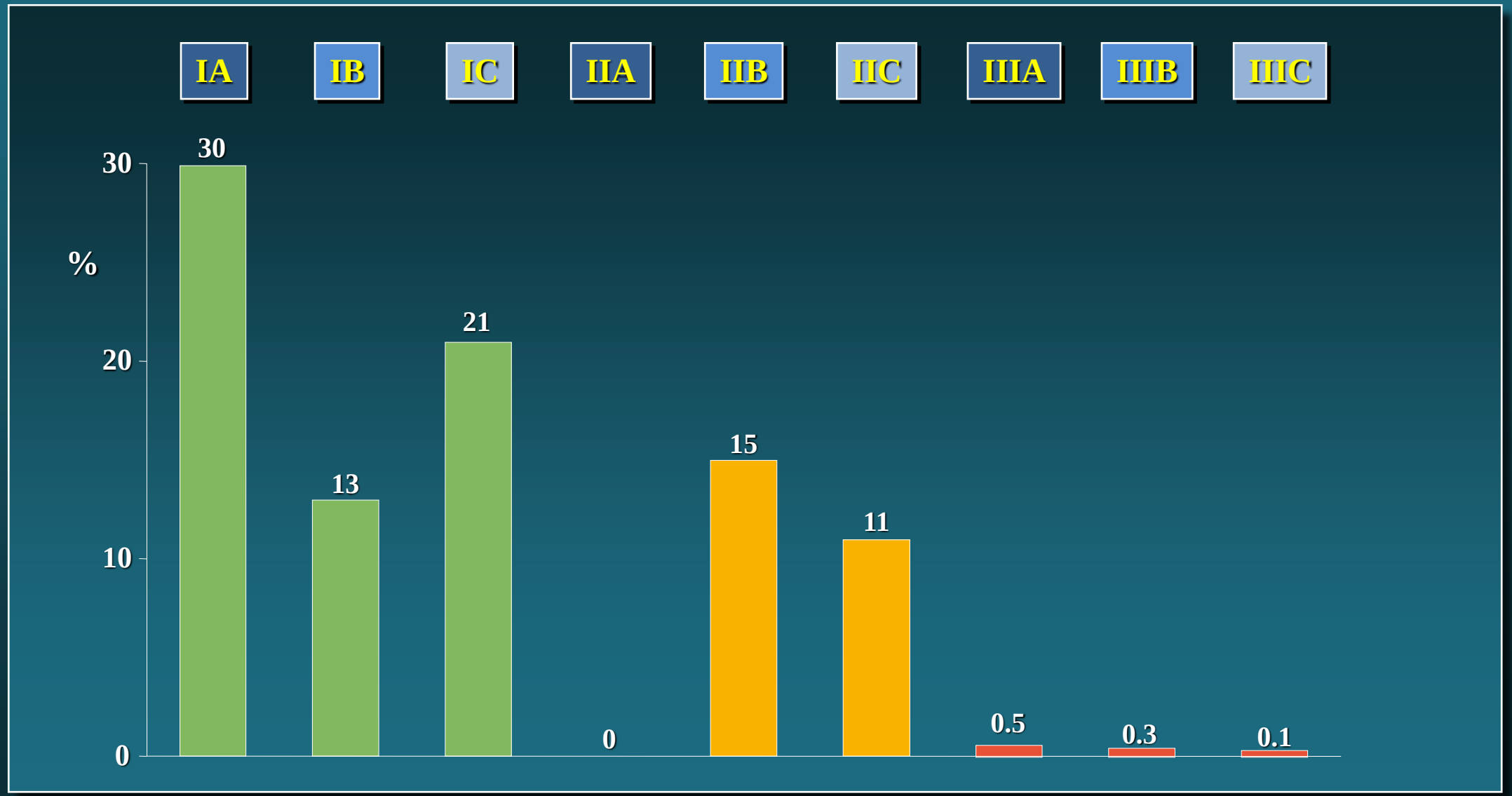
Major changes in the 2017 ACC/AHA GLs

- Grade 2 HT from 140mmHg SBP above(Grade 3 HT eliminated)
- High normal BP (130-139mmHg SBP) becomes Grade 1 HT
- Normal BP (120-129mmHg SBP) becomes BP elevation

BP threshold for drug treatment in 2017 ACC/AHA GLs

- Threshold >- 130/80mmHg in virtually all hypertensive patients, including old and very old (octogenarians) individuals
- Exception:No treatment if BP is high normal (130-139/85/89mmHg) and 10 year CV risk <10 %
- Just because of age old patients with a high normal BP usually have a 10year CV risk >10%

Distribution of class / level of evidence * in 2018 ESC/ESH Guidelines recommendations (n = 135)



* Subclasses IIa/b combined

Out-of-office BP in the 2017 ACC/AHA GLs

- Out-of office BP measurements are recommended for

  -Diagnosis of hypertension

  -Titration of BP-lowering interventions

- Some preference to Home vs Ambulatory BP

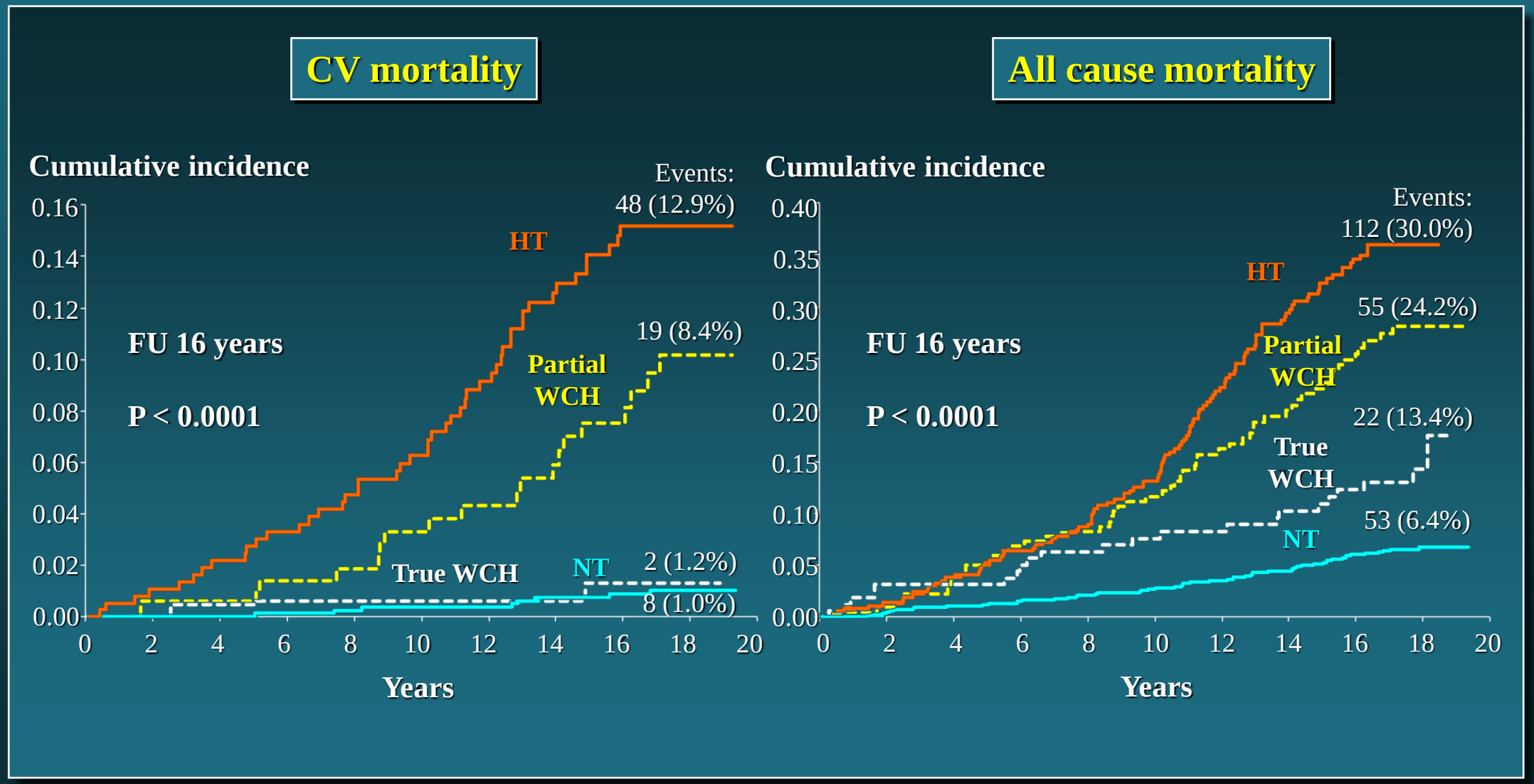
BP measurements

« In general, ABPM and HBPM should be regarded as complementary rather than absolute alternatives»

BP threshold for drug treatment in 2017 ACC/AHA GLs

- Threshold >- 130/80mmHg in all hypertensive patients, including old and very old (octogenarians) patients
- In patients with high normal BP and 10 year CV risk <10 %: threshold >-140/90mmHg

CV and All Cause Mortality in WCH Diagnosed by Normality of One (Partial WCH) or Both 24h and Home BP (True WCH)



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Mancia et al., Hypertension 2013, 62, 168

Home(H)/Ambulatory(A) BP. Major limitations

- **Advantage of HBP/ABP-guided T never tested**
- **Optimal HBP/ABP targets never established**
- **Evidence on long-term prognostic superiority of ABP/HBP over office BP limited by:**

  -Single set of ABP/HBP data

  -Adjustment approach

  -No verification of office BP quality

- **How much addition of HBP/ABP to office BP improves outcome prediction is unknown**

BP Thresholds for and Goals of Pharmacological Therapy in Patients With Hypertension According to Clinical Conditions

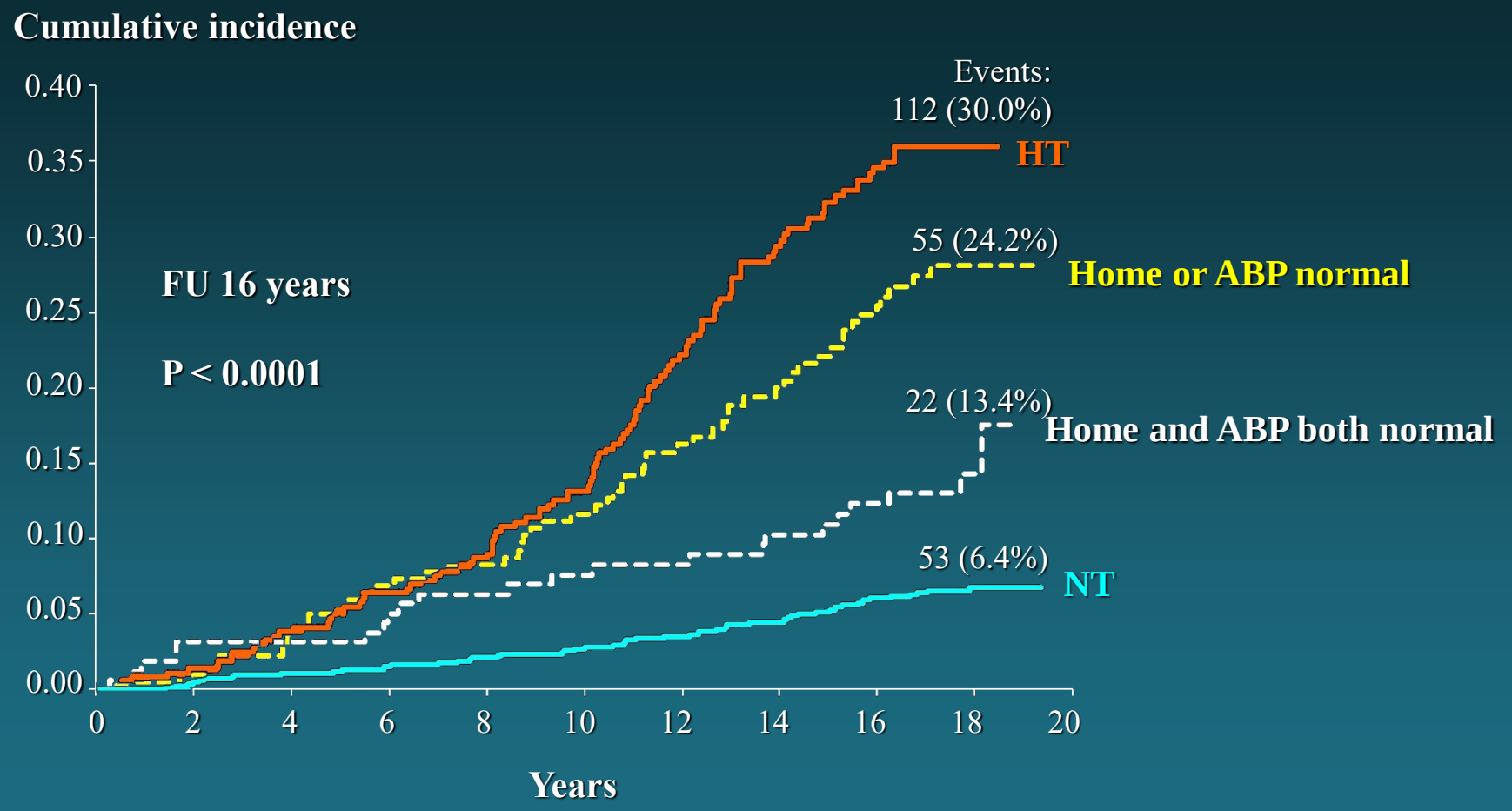
Clinical Condition(s)	BP Threshold, mm Hg	BP Goal, mm Hg
General		
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; noninstitutionalized, ambulatory, community-living adults)	≥130 (SBP)	<130 (SBP)
Specific comorbidities		
Diabetes mellitus	≥130/80	<130/80
Chronic kidney disease	≥130/80	<130/80
Chronic kidney disease after renal transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥140/90	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; and SBP, systolic blood pressure.

Drug treatment at high normal or grade 1 HT

- ESC/ESH GLs: Only in the setting of secondary prevention
- ACC/AHA GLs: When CV risk is greater than 10% (Framingham)

All cause mortality in WCH diagnosed by normality of both 24h home BP or of only one of these two BPs



Mancia et al., Hypertension 2013,62,168