I PERCORSI APPROPRIATI ASSISTENZIALI E TERAPEUTICI IN PREVENZIONE SECONDARIA

Approccio al paziente ad alto rischio cardiovascolare

10 GIUGNO 2022

CORSO WEBINAR

FAD SINCRONA

09.50-11.10 Round 2

Terapia di associazione nel paziente ad alto rischio cardiovascolare: dalle linee guida ESC al mondo reale. Come raggiungere i target?

Moderatori:

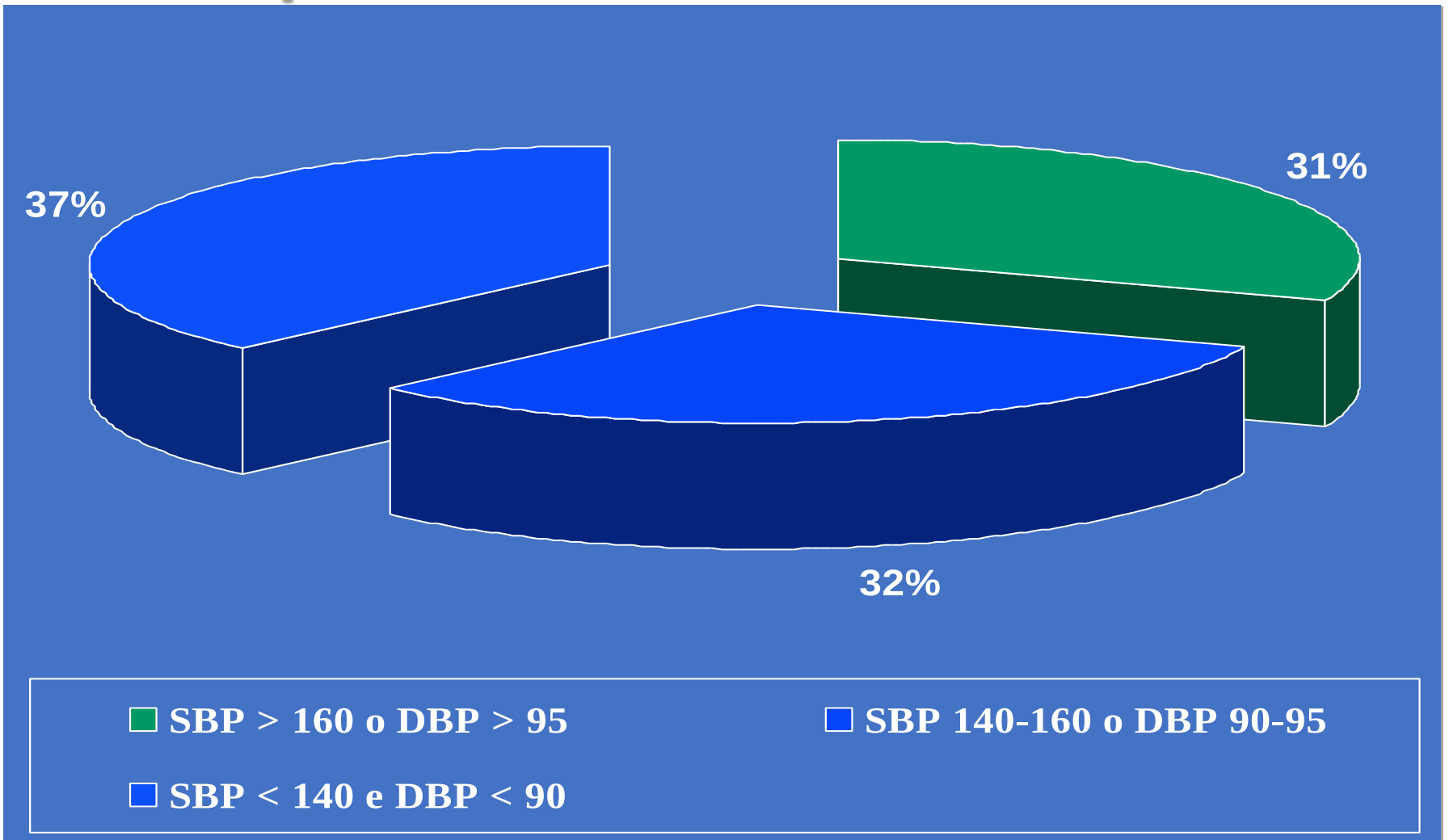
Giuseppe Pajes (Roma) - Luigi Sommariva (Viterbo)

Ipertensione arteriosa

M.G. Abrignani

U.O. di Cardiologia
P.O. S. Antonio Abate di Trapani
ASP Trapani

Lo studio SILVIA: Studio Italiano Longitudinale sulla Valutazione dell'Ipertensione Arteriosa nel 2000



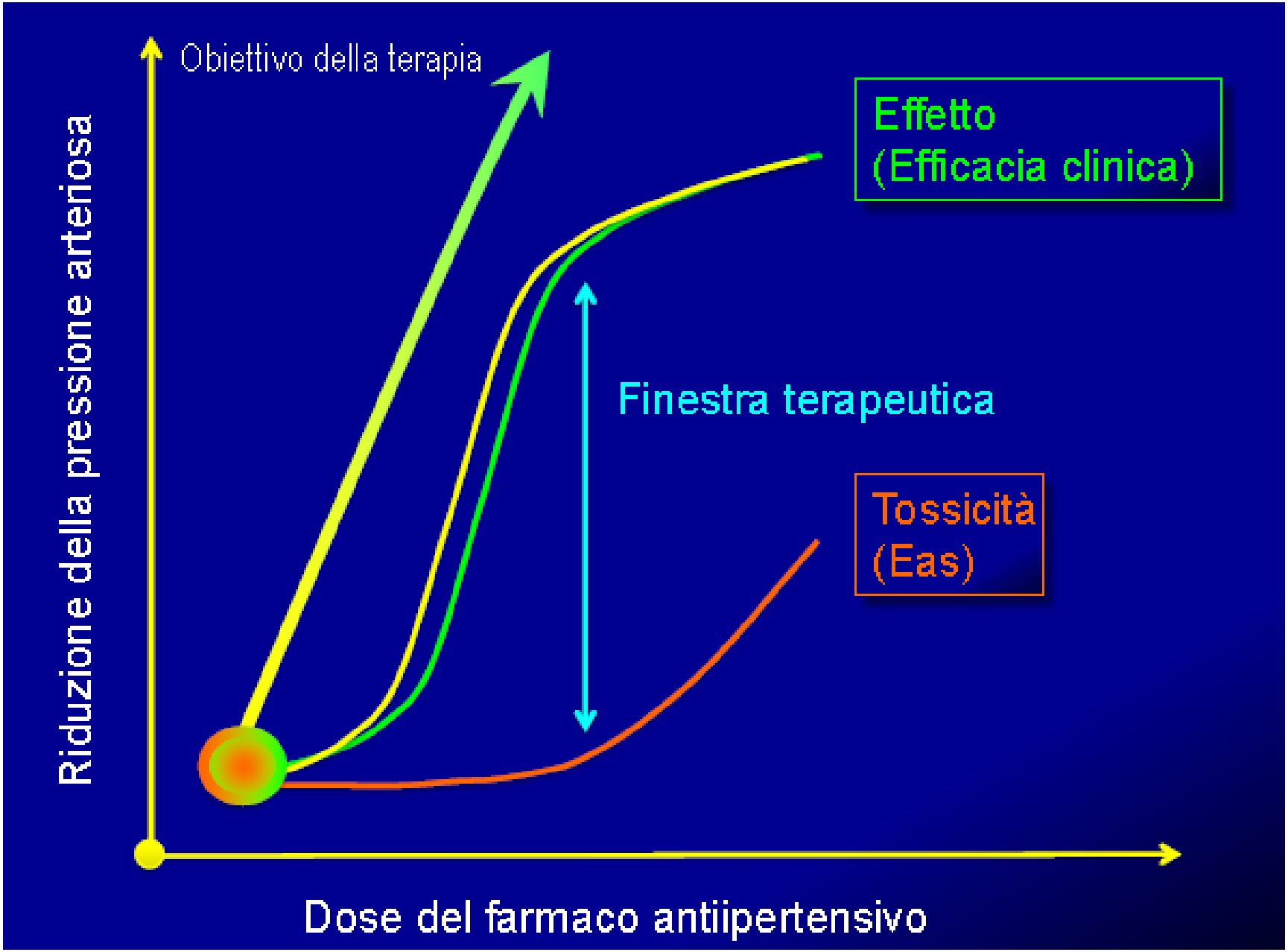
ESC European Society of Cardiology
European Heart Journal (2019) 0, 1–12
doi:10.1093/eurheartj/ehz300

May Measurement Month 2018: a pragmatic global screening campaign to raise awareness of blood pressure by the International Society of Hypertension

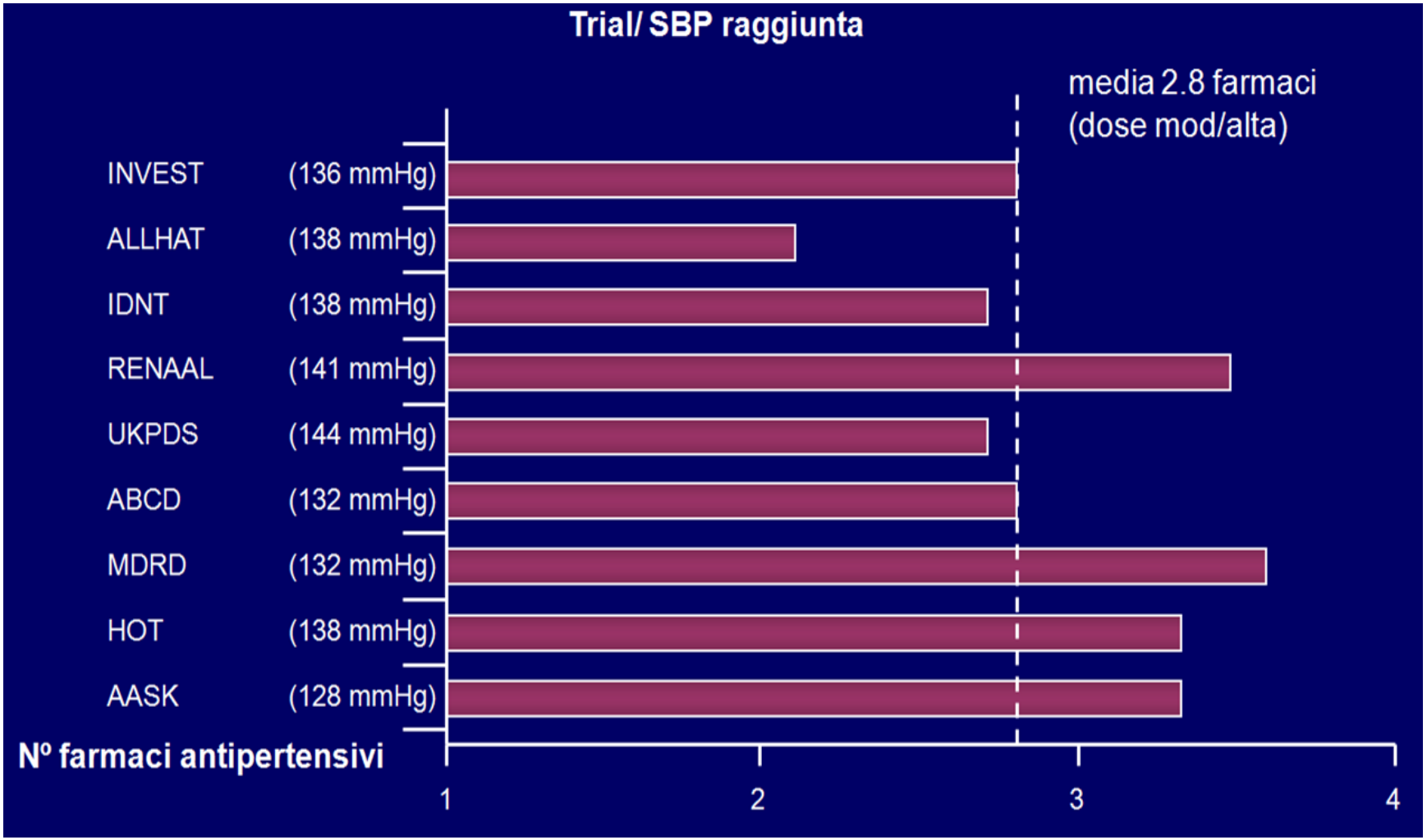
Thomas Beaney [1,2], Louise M. Burrell [3], Rafael R. Castillo[4], Fadi J. Charchar [5], Suzie Cro [1], Albertino Damasceno [6], Ruan Kruger [7,8], Peter M. Nilsson [9], Dorairaj Prabhakaran [10], Agustin J. Ramirez[11], Markus P. Schlaich [12], Aletta E. Schutte [7,8], Maciej Tomaszewski [13], Rhian Touyz [14], Ji-Guang Wang [15], Michael A. Weber [16], and Neil R. Poulter [1]*; on behalf of the MMM Investigators

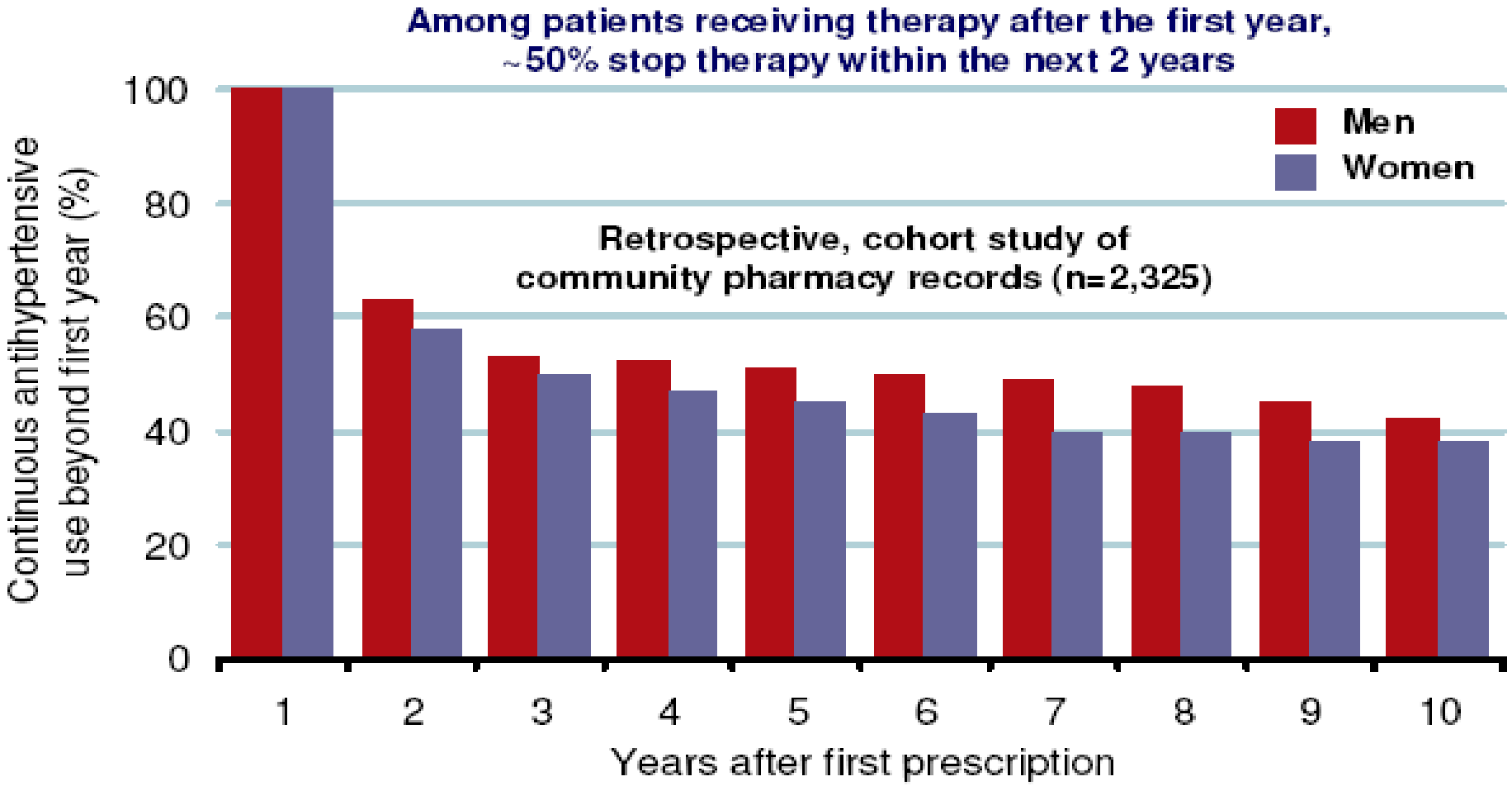
Table 4 Key proportions for participants with hypertension, worldwide, and by region, after imputation

Region	Number with hypertension	Proportion with hypertension (%)	Proportion of hypertensives aware (%)	Proportion of hypertensives on medication (%)	Proportion of those on medication with controlled BP (%)	Proportion of all hypertensives controlled (%)
South Asia	132 173	33.8	59.5	56.9	70.4	40.0
East Asia	93 499	30.7	64.0	59.1	63.2	37.3
South-East Asia and Australasia	104 148	35.4	50.8	50.1	48.7	24.4
Americas	76 574	40.4	76.7	70.6	60.9	43.0
Sub-Saharan Africa	37 603	24.8	43.6	33.1	45.1	15.0
Northern Africa and Middle East	24 579	26.3	35.7	32.1	58.6	18.8
Europe	33 504	41.6	71.0	62.0	48.9	30.3
Worldwide	**502 079**	**33.4**	**59.5**	**55.3**	**60.0**	**33.2**


Obiettivo della terapia
Riduzione della pressione arteriosa
Effetto
(Efficacia clinica)
Finestra terapeutica
Tossicità
(Eas)
Dose del farmaco antiipertensivo

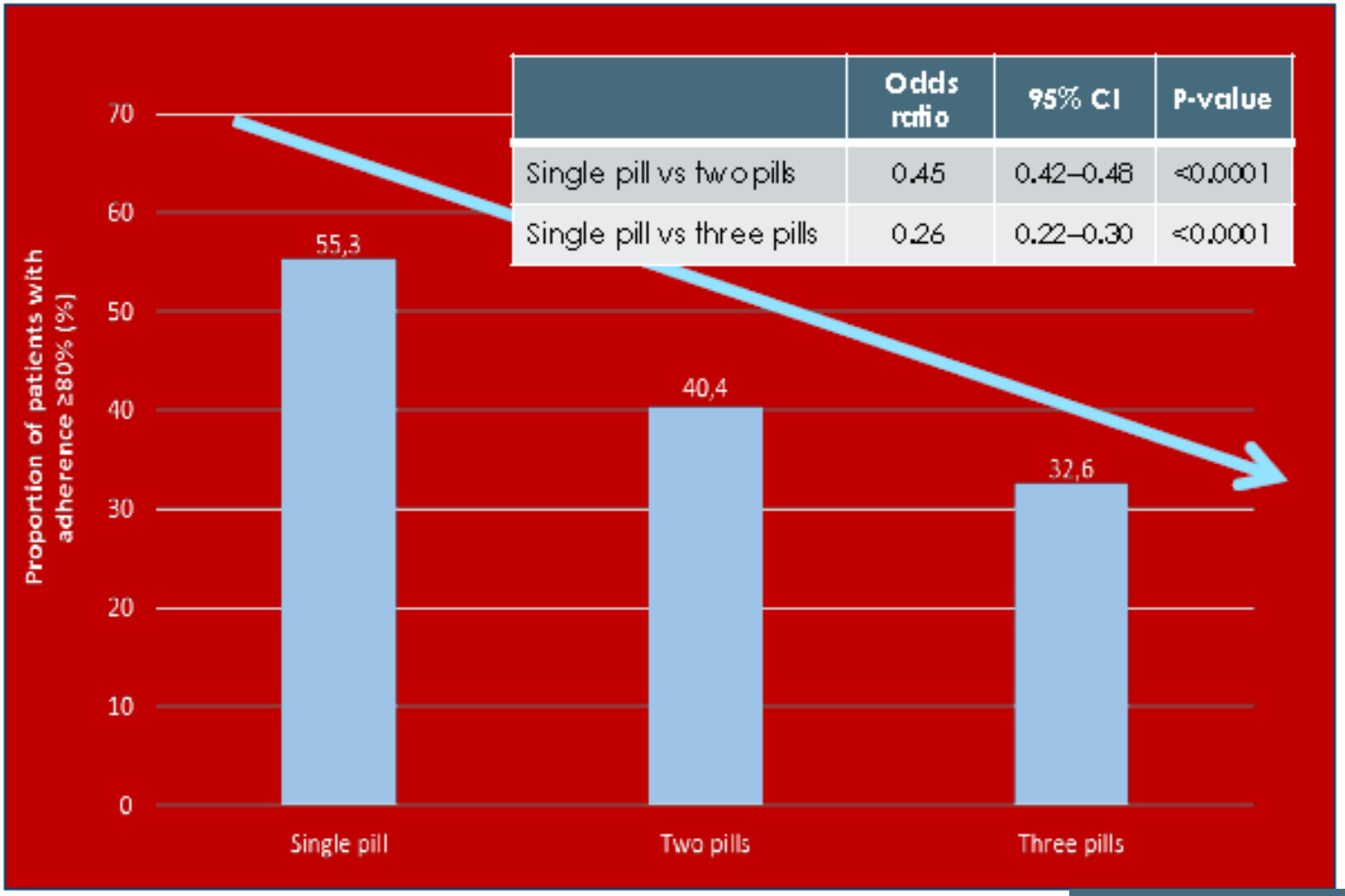
Per raggiungere gli obiettivi pressori è necessaria una terapia con più farmaci





Van Wijk et al. J Hypertens 2005;23:2101–7

Single-pill fixed-dose combinations are associated with greater adherence in hypertension



	Odds ratio	95% CI	P-value
Single pill vs two pills	0.45	0.42–0.48	<0.0001
Single pill vs three pills	0.26	0.22–0.30	<0.0001

Xie et al. CMRO 2014;30:2415–22

Management of arterial hypertension: Transfer from clinical guidelines into daily practice – Results of a survey in German practitioners offices

Hans-Georg Predel[1], Fabian Graas[2], Georg Rudinger[2], Olaf Randerath[3]

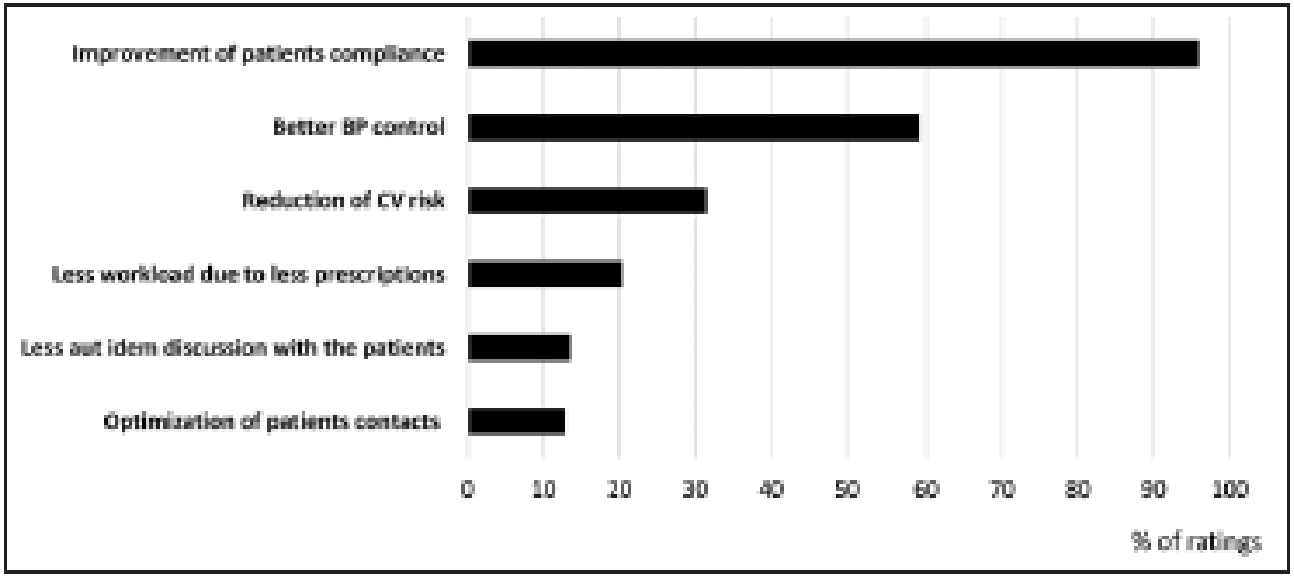
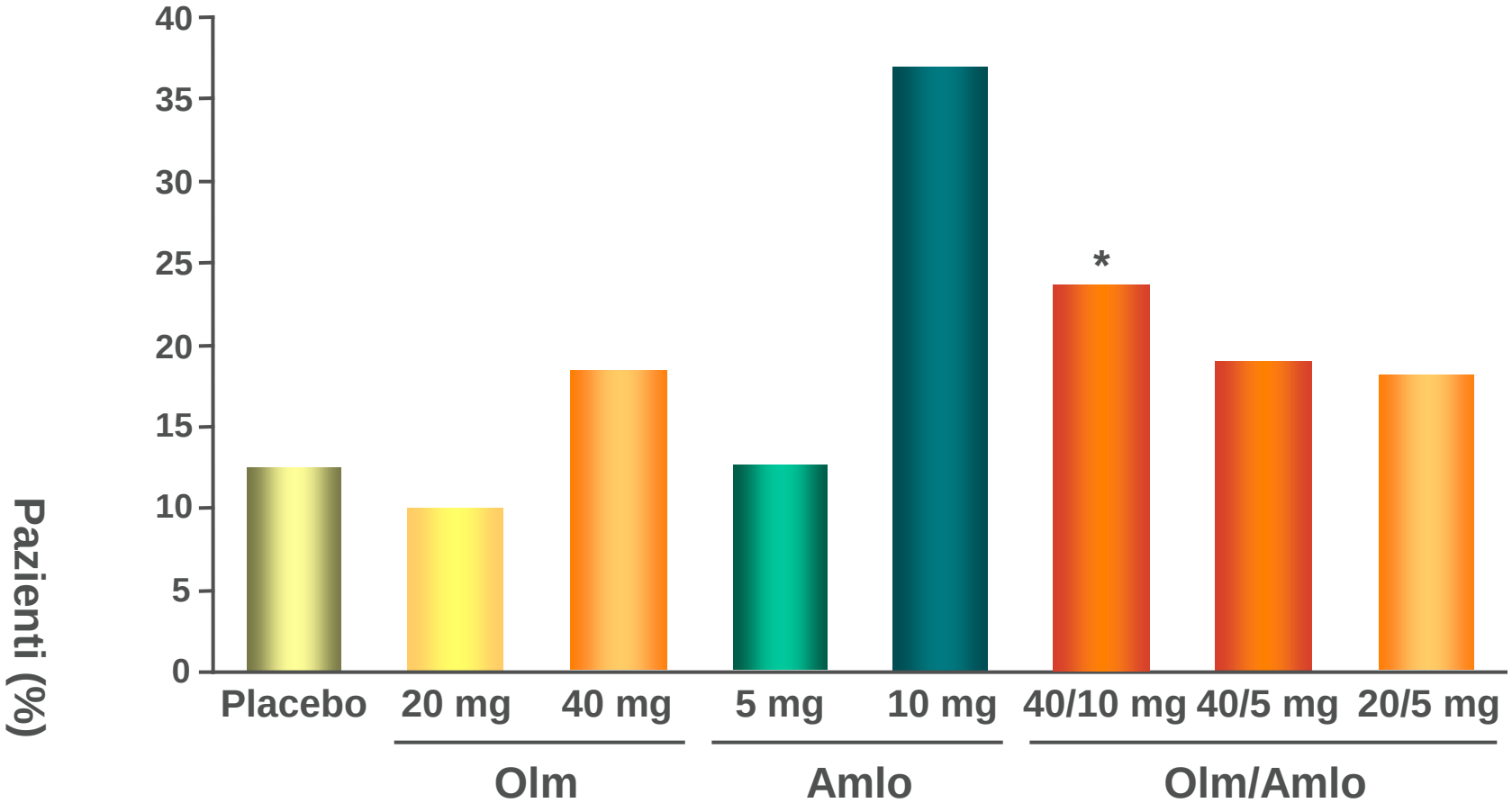


Figure 2: Advantages of a single pill (SP) treatment regimen (three different answers allowed)

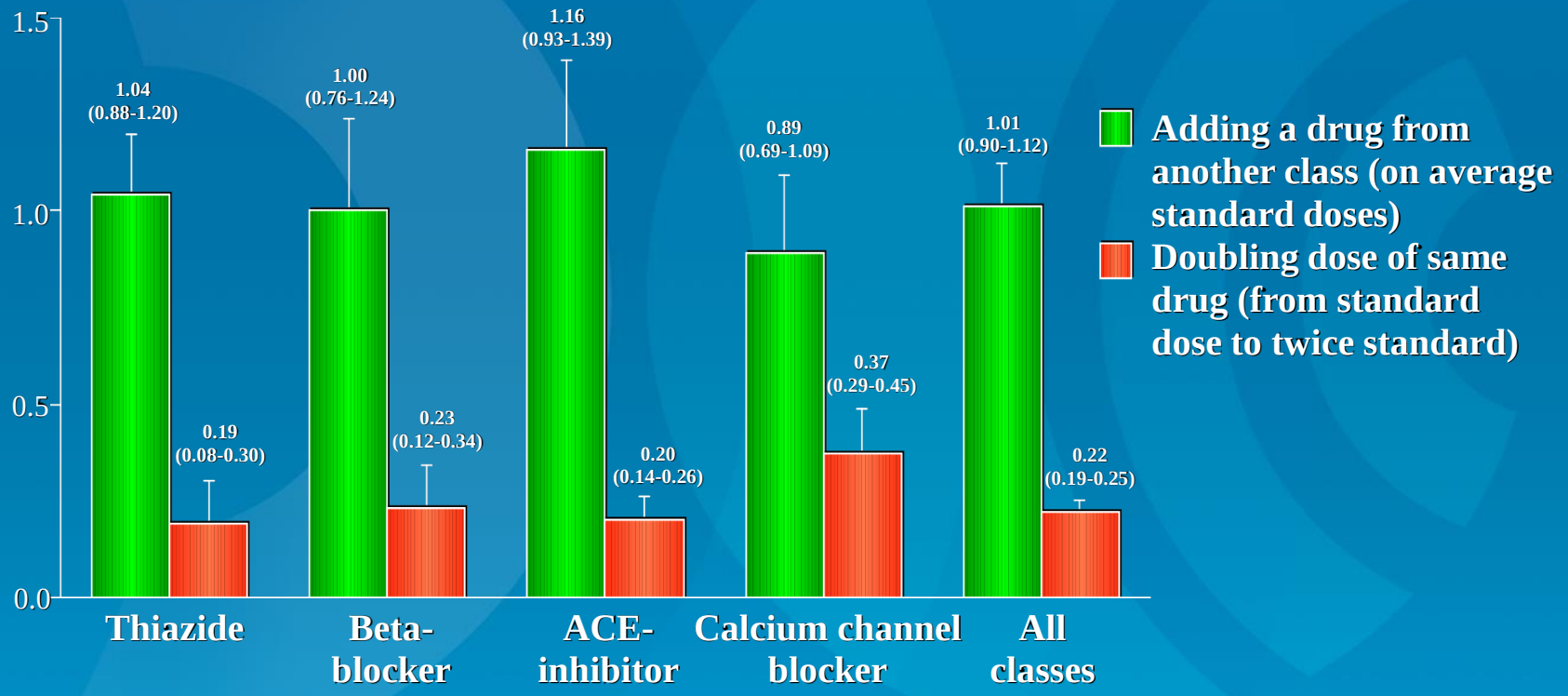
Incidenza di edemi declivi in pazienti ipertesi trattati con olmesartan/amlodipina



*p=0.0011 vs Amlo 10 mg/die

Sanford M et al. Drugs 2009; 69: 717-29

Incremento di effetto ipotensivo osservato/atteso ottenuto aggiungendo un farmaco o raddoppiando la dose rispetto alla classe terapeutica

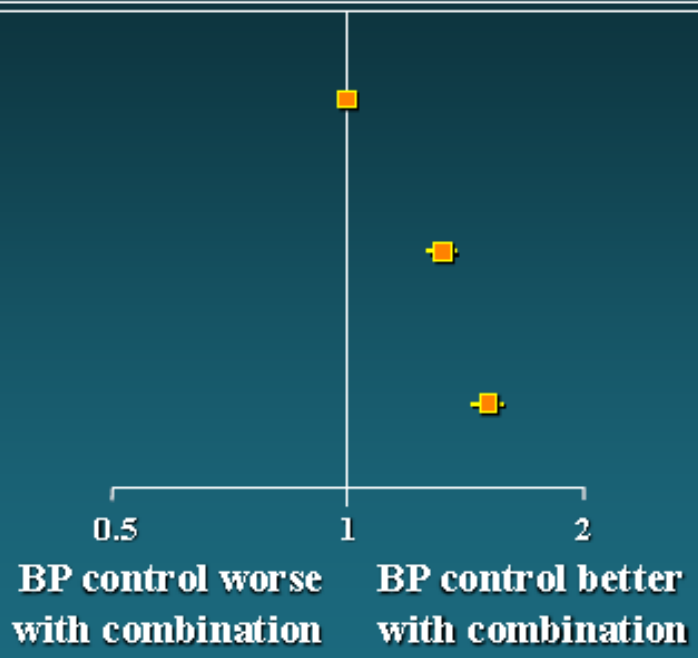


* The expected incremental effect is the incremental blood pressure reduction of the added (or doubled drug), assuming an additive effect and allowing for the smaller reduction from 1 drug (or dose of 1 drug) given the lower pretreatment blood pressure because of the other

Wald DS et al., Am J Med 2009; 122: 290

Increased Chance of BP Control over 1 Year by Initial Combination Therapy vs Monotherapy + Add-on Treatment

Initial TP	n	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Monotherapy	79099		Ref
Free Combination	18329		1.34 (1.31-1.37)
Single Pill Combination	9194		1.53 (1.47-1.58)



Egan BE et al., Hypertension 2012; 59: 1124-1131

PLOS ONE

RESEARCH ARTICLE

Free versus Fixed Combination Antihypertensive Therapy for Essential Arterial Hypertension: A Systematic Review and Meta-Analysis

Samir G. Mallat[1☯], Bassem Y. Tanios[1☯*], Houssam S. Itani[2☯], Tamara Lotfi[3‡], Elie A. Akl[4‡]

Study or Subgroup	Fixed Combination Mean	SD	Total	Free Combination Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Asplund 1984	6.8	7.5	80	8.3	7.7	80	18.5%	-0.20 [-0.51, 0.11]
Jaatela 1978	136	9.5	21	135	9.5	21	13.4%	0.10 [-0.50, 0.71]
McLay 2000	140	5	25	141	5	25	14.2%	-0.20 [-0.75, 0.36]
Nissinen 1980	136.9	9.5	23	137.3	9.5	23	13.8%	-0.04 [-0.62, 0.54]
Olvera 1991	141	18	14	139	24	15	11.4%	0.09 [-0.64, 0.82]
Pecherina 2014	115.8	9.5	62	125.6	9.5	62	17.4%	-1.03 [-1.40, -0.65]
Solomon 1980	144.9	9.5	14	142.9	9.5	14	11.2%	0.20 [-0.54, 0.95]
Total (95% CI)			**239**			**240**	**100.0%**	**-0.20 [-0.56, 0.16]**

Heterogeneity: Tau² = 0.16; Chi² = 20.26, df = 6 (P = 0.002); I² = 70%
Test for overall effect: Z = 1.10 (P = 0.27)

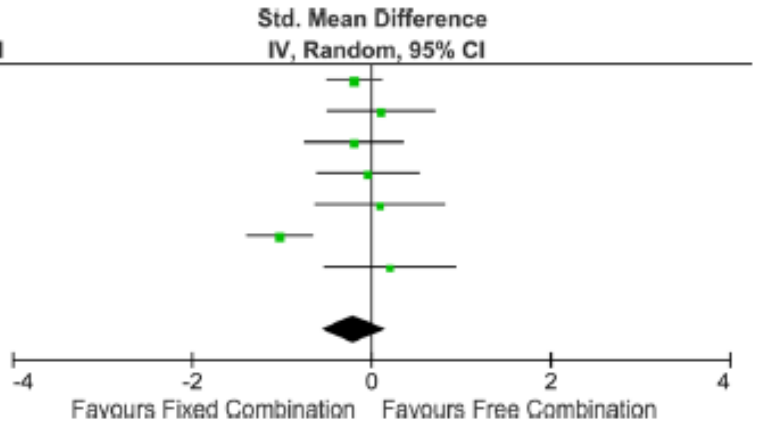
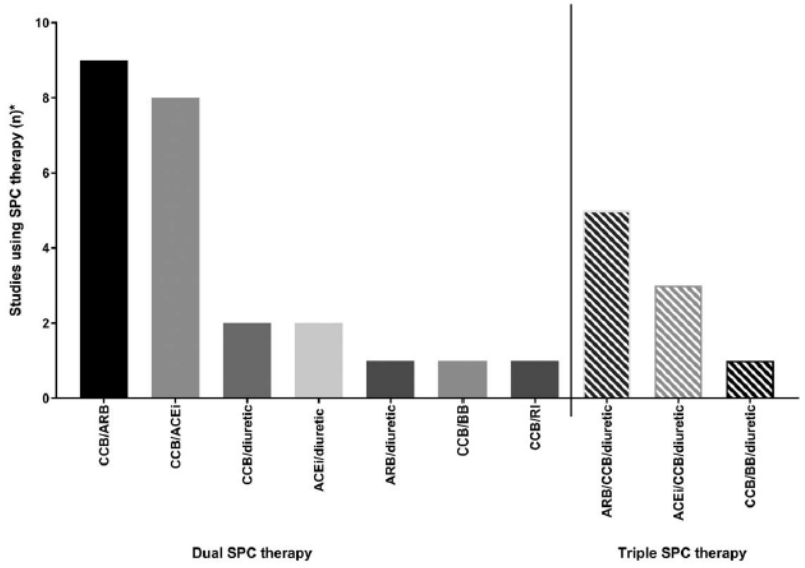


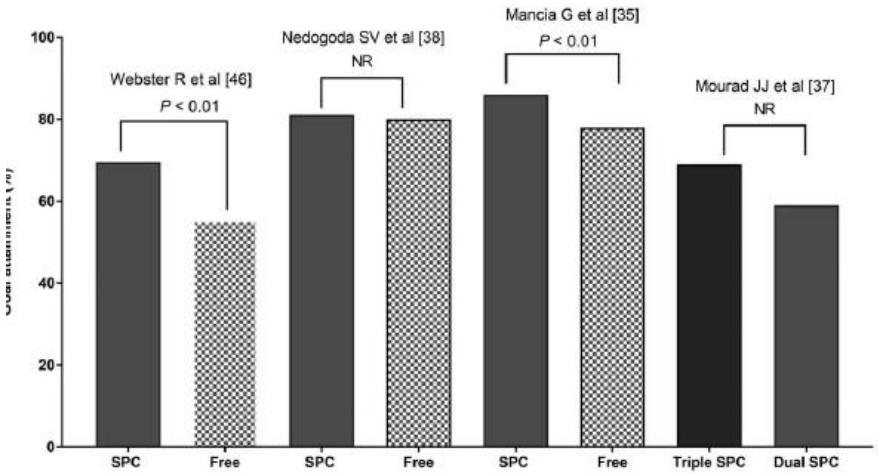
Fig 4. Forest plot for the effect of fixed vs. free antihypertensive drug therapy on mean systolic blood pressure, using standardized mean difference.

Impact of single-pill combination therapy on adherence, blood pressure control, and clinical outcomes: a rapid evidence assessment of recent literature

Konstantinos Tsioufis[a], Reinhold Kreutz[b], Georgia Sykara[c], Joris van Vugt[d], and Tarek Hassan[e]

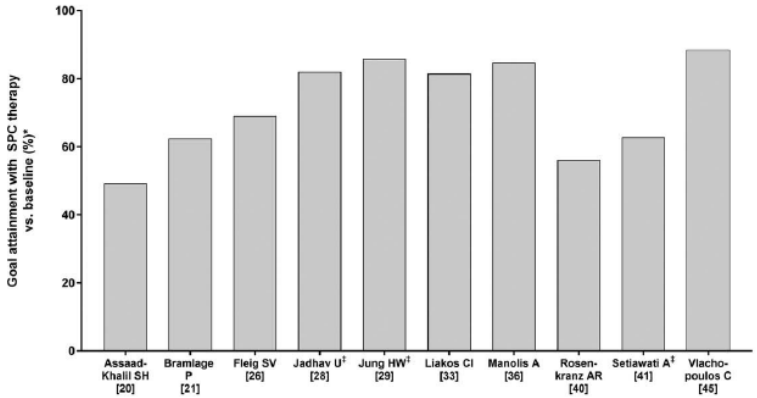


RCT studies



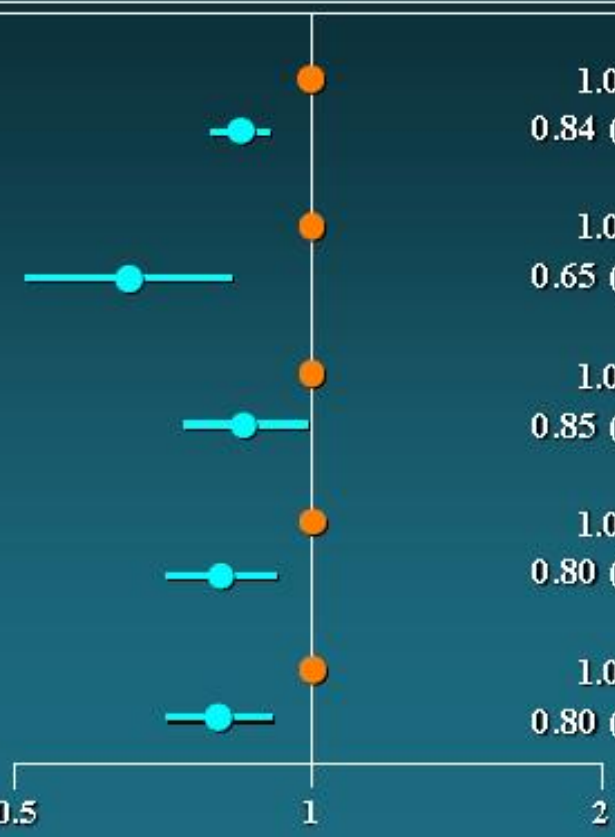
BP goal was <140/90 mmHg.
Webster R et al [46] and Mancia G et al [35] reported after 6-months' follow-up. Nedogoda SV et al [38] and Mourad JJ et al [37] reported after 3-months' follow-up.
NR = not reported.

(b) **Observational studies**



Risk of CV events over a 3 year FU in pts on initial FDC or monotherapy largely failing to move to combination therapy due to therapeutic inertia (PS analysis)

Outcome	Treatment strategy	HR (95% CI)	p
Any CV events	Monotherapy	1.00 (Ref)	<0.001
	Combination therapy	0.84 (0.79-0.90)	
Heart failure	Monotherapy	1.00 (Ref)	<0.001
	Combination therapy	0.65 (0.51-0.82)	
Cerebrovascular disease	Monotherapy	1.00 (Ref)	0.027
	Combination therapy	0.85 (0.74-0.98)	
Ischemic heart disease	Monotherapy	1.00 (Ref)	<0.001
	Combination therapy	0.80 (0.71-0.91)	
Death	Monotherapy	1.00 (Ref)	<0.001
	Combination therapy	0.80 (0.72-0.89)	



Rea, Corrao, Merlino, Mancia, Hypertension, 2018

Non tutte le combinazioni sono uguali

Attenzione a queste associazioni di farmaci antiipertensivi!

Associazione di farmaci con differente meccanismo d'azione senza effetto ipotensivo additivo

- Diuretico + calcio-antagonista (possibile associazione con diuretico dell'ansa in pazienti con insufficienza renale)
- Beta-bloccante + ACE-inibitore (e AT1-antagonista)

Associazione di farmaci con interazione negativa sull'effetto ipotensivo

- Alfa$_1$-antagonista + clonidina

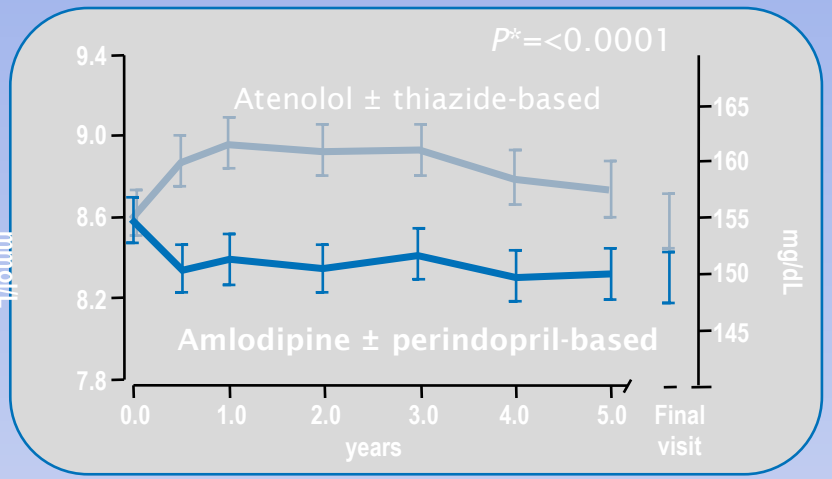
Associazione di farmaci antiipertensivi potenzialmente pericolosa

- Beta-bloccante + clonidina
- Beta-bloccante + calcio-antagonista non-DHP

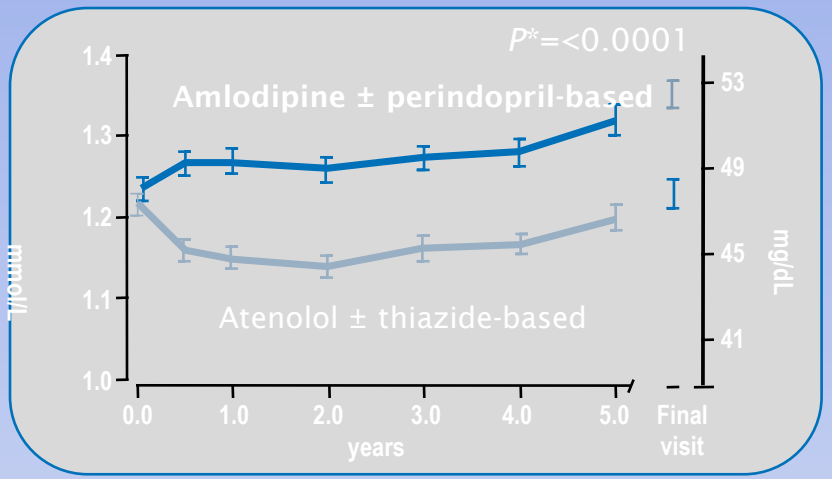
Svantaggi dell'associazione atenololo/diuretico tiazidico:

Effetti Metabolici

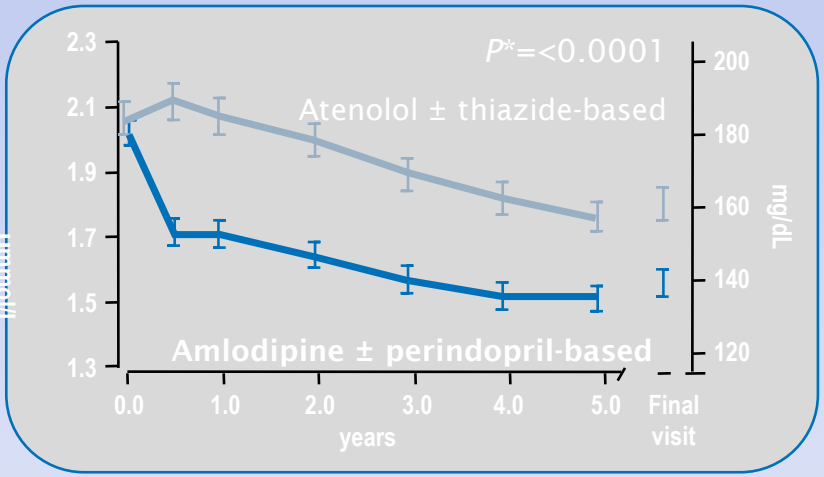
Glucosio



High-density lipoprotein-cholesterol



Trigliceridi



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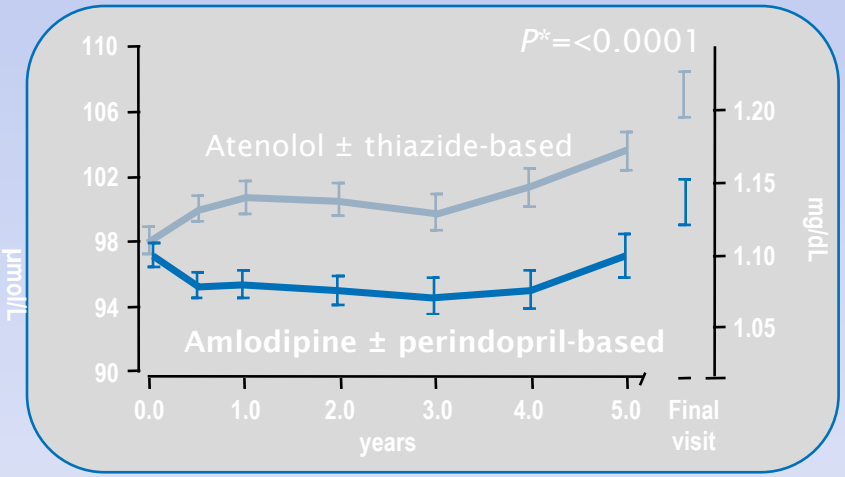
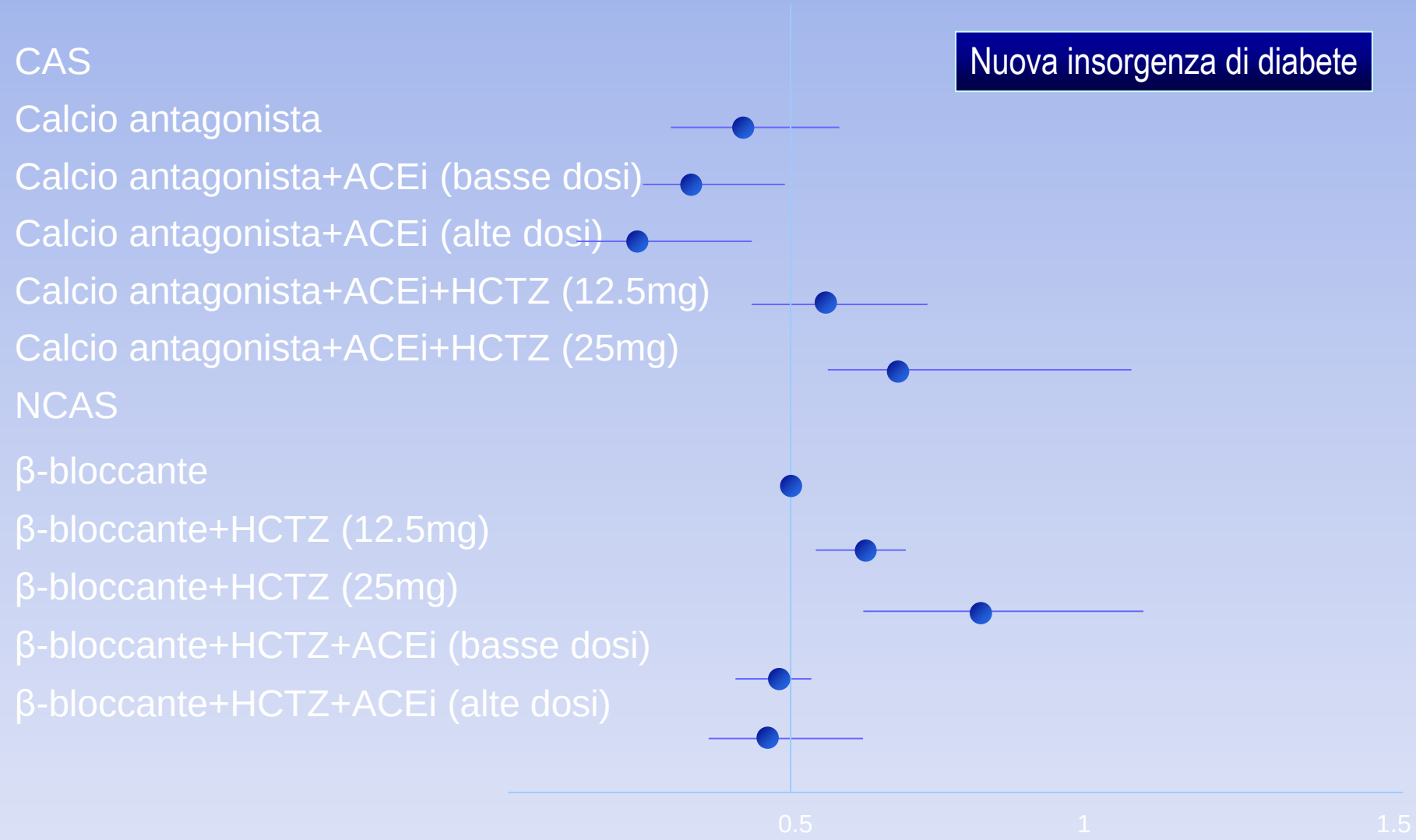


T-test performed on accumulated mean area under curve. Adapted from *J Hypertens*. 2008;26(11):2103-2111.

Effetti metabolici di diversi farmaci antiipertensivi



JAMA. 2003;290;2805-2816

Hindawi
International Journal of Hypertension
Volume 2020, Article ID 3097198, 8 pages
https://doi.org/10.1155/2020/3097198

Research Article

Effect of Different Blood-Pressure-Lowering Regimens on the Blood Pressure Control among Hypertensive Patients Treated in Hospital Conditions

Anna Paczkowska,[1] **Karolina Hoffmann**,[2] **Krzysztof Kus**,[1] **Dorota Kopciuch**,[1] **Tomasz Zaprutko**,[1] **Piotr Ratajczak**,[1] **Elżbieta Nowakowska**,[1] **and Wiesław Bryl**[2]

Table 5: Evaluation of efficacy of hypertension treatment in hospital environment according to the most common pharmacotherapy regimens.

Pharmacotherapy regimen	Number of patients on the pharmacotherapy regimen	Blood pressure measurement upon admission to the hospital		Blood pressure measurement upon discharge from the hospital		Blood pressure control (<130/80 mmHg) %
		Average systolic blood pressure values (mmHg, SEM ± SD)	Average diastolic blood pressure values (mmHg, SEM ± SD)	Average systolic blood pressure values (mmHg, SEM ± SD)	Average diastolic blood pressure values (mmHg, SEM ± SD)	
β-blockers + ACEI (A)	19 (9.3%)	156.26 ± 12.04	94.37 ± 7.83	122.37 ± 9.06 $\$p^* < 0.001$	73.63 ± 12.68 $\$p < 0.001$	87.50 $\&p = 0.0381$ $\hat{}p = 0.0006$
Diuretics + ACEI (B)	19 (9.3%)	157.21 ± 9.46	92.68 ± 8.01	124.26 ± 9.42 $\$p < 0.001$	76.79 ± 8.7 $\$p < 0.001$	76.47 $\hat{}p = 0.0077$
β-blockers + diuretics + calcium channel antagonist (C)	54 (26.47%)	163.67 ± 14.12 $*p = 0.0454$	94.61 ± 11.34	131.31 ± 12.30 $*p = 0.0049$ $\#p = 0.0261$ $\$p < 0.0001$	79.43 ± 6.97 $*p = 0.015$ $\$p < 0.0001$	61.81 $\hat{}p = 0.0324$
ACEI + diuretics + ARBs (D)	25 (12.25%)	182.00 ± 23.06 $*p < 0.0001$ $\#p < 0.0001$ $\&p < 0.0001$	103.32 ± 19.74 $\#p = 0.0326$ $\&p = 0.0151$	136.24 ± 16.25 $*p = 0.0018$ $\#p = 0.0065$ $\$p < 0.0001$	82.80 ± 8.95 $*p = 0.0074$ $\#p = 0.0311$ $\$p < 0.0001$	36.00

ESC European Society of Cardiology
European Heart Journal (2018) 39, 3021–3104
doi:10.1093/eurheartj/ehy339

2018 ESC/ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)

Authors/Task Force Members: Bryan Williams* (ESC Chairperson) (UK),

Table 21 Major drug combinations used in trials of antihypertensive treatment in a stepped approach or as a randomized combination (combinations vs. placebo or monotherapy)

Trial	Comparator	Type of patients	SBP difference (mmHg)	Outcomes [change in relative risk (%)]
ACE inhibitor and diuretic combination				
PROGRESS[227]	Placebo	Previous stroke or TIA	−9	−28% strokes ($P < 0.001$)
ADVANCE[229]	Placebo	Diabetes	−5.6	−9% micro/macrovascular events ($P = 0.04$)
HYVET[220]	Placebo	Hypertensive; >80 years	−15	−34% CV events ($P < 0.001$)
ARB and diuretic combination				
SCOPE[330]	Diuretic + placebo	Hypertensive; >70 years	−3.2	−28% non fatal strokes ($P = 0.04$)
CCB and diuretic combination				
FEVER[331]	Diuretic + placebo	Hypertensive	−4	−27% CV events ($P < 0.001$)
ACE inhibitor and CCB combination				
Syst Eur[332]	Placebo	Older with ISH	−10	−31% CV events ($P < 0.001$)
Syst China[333]	Placebo	Older with ISH	−9	−37% CV events ($P < 0.004$)
Beta-blocker and diuretic combination				
Coope and Warrender[322]	Placebo	Older hypertensive	−18	−42% strokes ($P < 0.03$)
SHEP[323]	Placebo	Older with ISH	−13	−36% strokes ($P < 0.001$)
STOP H[324]	Placebo	Older hypertensive	−23	−40% CV events ($P = 0.003$)
STOP H 2[334]	ACE inhibitor or conventional antihypertensive	Hypertensive	0	NS difference in CV events
Combination of two RAS blockers/ACE inhibitor + ARB or RAS blocker + renin inhibitor)				
ONTARGET[299]	ACE inhibitor or ARB	High risk patients		More renal events
ALTITUDE[291]	ACE inhibitor or ARB	High risk diabetic patients		More renal events

Table 11 Major drug combinations used in trials of antihypertensive treatment in a stepped approach or as a randomized combination (combinations vs. other combinations)

Trial	Comparator	Type of patients	SBP difference (mmHg)	Outcomes (change in relative risk (%))
ACE inhibitor and diuretic combination				
CAPP[228]	BB + diuretic	Hypertensive	+3	+3% CV events (NS)
ACCOMPLISH[227]	ACE inhibitor + CCB	Hypertensive with risk factors	+1	+21% CV events ($P < 0.001$)
ARB and diuretic combination				
LIFE[230]	BB + diuretic	Hypertensive with LVH	−1	−26% strokes ($P < 0.001$)
CCB and diuretic combination				
ELSA[234]	BB + diuretic	Hypertensive	0	NS difference in CV events
CONVINCE[233]	BB + diuretic	Hypertensive with risk factors	0	NS difference in CV events
VALUE[237]	ARB + diuretic	High-risk hypertensive	−2.2	−3% CV events (P = NS)
COPE[223]	CCB + BB	Hypertensive	+0.7	NS difference in CV events or stroke
ACE inhibitor and CCB combination				
NORDIL[239]	BB + diuretic	Hypertensive	+3	NS difference in CV events
INVEST[240]	BB + diuretic	Hypertensive with CAD	0	NS difference in CV events
ASCOT[270]	BB + diuretic	Hypertensive with risk factors	−3	−16% CV events ($P < 0.001$)
ACCOMPLISH[227]	ACE inhibitor + diuretic	Hypertensive with risk factors	−1	−21% CV events ($P < 0.001$)
Beta-blocker and diuretic combination				
CAPP[228]	ACE inhibitor + diuretic	Hypertensive	−3	−3% CV events (P = NS)
LIFE[230]	ARB + diuretic	Hypertensive with LVH	+1	+25% strokes ($P < 0.001$)
ALLHAT[274]	ACE inhibitor + BB	Hypertensive with risk factors	−2	NS difference in CV events
ALLHAT[274]	CCB + BB	Hypertensive with risk factors	−1	NS difference in CV events
CONVINCE[233]	CCB + diuretic	Hypertensive with risk factors	0	NS difference in CV events
NORDIL[239]	ACE inhibitor + CCB	Hypertensive	−3	NS difference in CV events
INVEST[240]	ACE inhibitor + CCB	Hypertensive with CAD	0	NS difference in CV events
ASCOT[270]	ACE inhibitor + CCB	Hypertensive with risk factors	+3	+16% CV events ($P < 0.001$)
Beta-blocker and CCB combination				
COPE[223]	ARB + CCB	Hypertensive	+0.8	NS difference in CV events or stroke
ARB and CCB combination				
COPE[223]	CCB + diuretic	Hypertensive	−0.7	NS difference in CV events or stroke
COPE[223]	CCB + BB	Hypertensive	−0.8	NS difference in CV events or stroke
CONAN[233]	ARB + diuretic	Older hypertensive	0	NS difference in CV events

ESC European Society of Cardiology
European Heart Journal (2018) 39, 3021–3104
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2018 ESC/ESH Guidelines for the management of arterial hypertension

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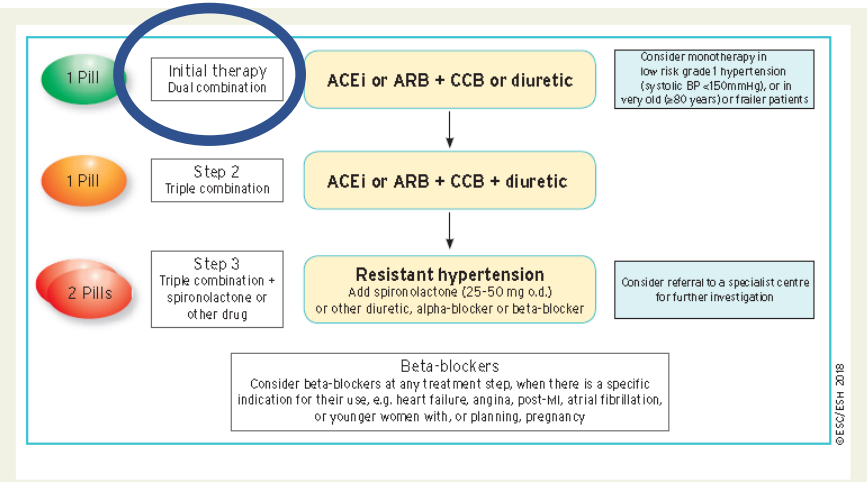

Figure 4 Core drug treatment strategy for uncomplicated hypertension. The core algorithm is also appropriate for most patients with HMOD, cerebrovascular disease, diabetes, or PAD. ACEi angiotensin-converting enzyme inhibitor; ARB angiotensin receptor blocker; CCB calcium channel blocker; HMOD hypertension-mediated organ damage; MI myocardial infarction; o.d. omni die (every day); PAD peripheral artery disease.

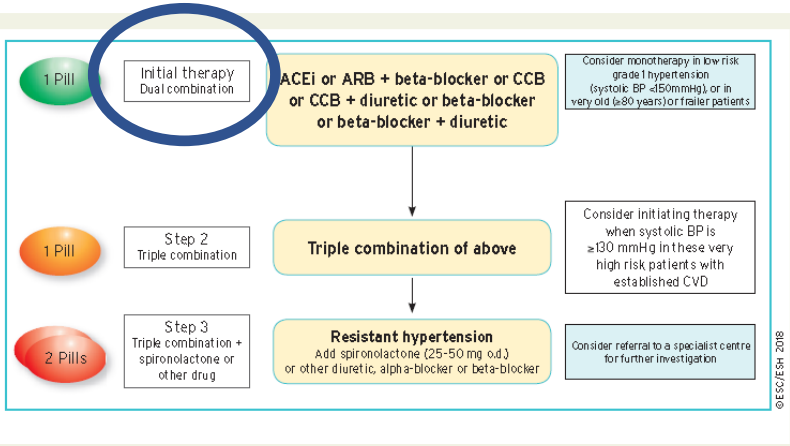

Figure 5 Drug treatment strategy for hypertension and coronary artery disease. ACEi angiotensin-converting enzyme inhibitor; ARB angiotensin receptor blocker; BP blood pressure; CCB calcium channel blocker; CVD cardiovascular disease; o.d. omni die (every day).

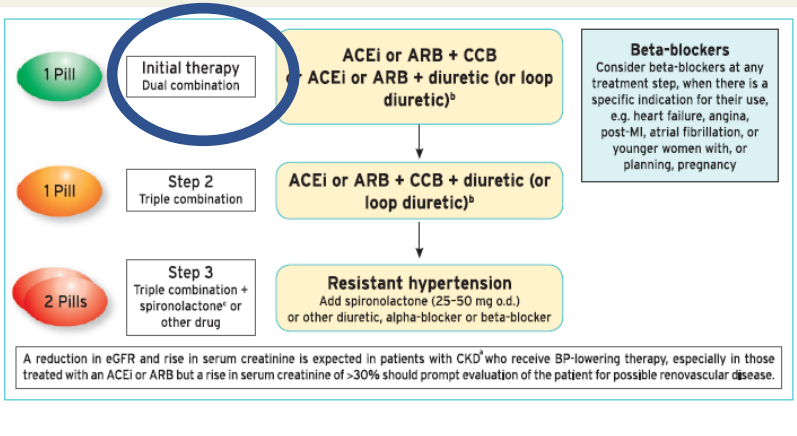

Figure 6 Drug treatment strategy for hypertension and chronic kidney disease. ACEi angiotensin-converting enzyme inhibitor; ARB angiotensin receptor blocker; BP blood pressure; CCB calcium channel blocker; CKD chronic kidney disease; eGFR estimated glomerular filtration rate; MI myocardial infarction; o.d. omni die (every day).

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The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)

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Drug treatment strategy for hypertension

Recommendations	Class[a]	Level[b]
Among all antihypertensive drugs, ACE inhibitors, ARBs, beta-blockers, CCBs, and diuretics (thiazides and thiazide-like drugs such as chlorthalidone and indapamide) have demonstrated effective reduction of BP and CV events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies.[2]	I	A
Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used.[233,318,327,329,341 345]	I	A
It is recommended that beta-blockers are combined with any of the other major drug classes when there are specific clinical situations, e.g. angina, post-myocardial infarction, heart failure, or heart rate control.[300,341]	I	A
It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in an SPC. Exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is <150 mmHg).[342,346,351]	I	B
It is recommended that if BP is not controlled[c] with a two-drug combination, treatment should be increased to a three-drug combination, usually a RAS blocker with a CCB and a thiazide/thiazide-like diuretic, preferably as an SPC.[349,350]	I	A
It is recommended that if BP is not controlled[c] with a three-drug combination, treatment should be increased by the addition of spironolactone or, if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, a beta-blocker, or an alpha-blocker.[310]	I	B
The combination of two RAS blockers is not recommended.[291,298,299]	III	A

Criteri per l'associazione di farmaci antiipertensivi

- Associare farmaci con lo stesso profilo farmacocinetico in termini di tempo di picco e di durata d'azione
- Associare farmaci che abbiano meccanismi d'azione diversi, ma complementari
- L'efficacia antiipertensiva dell'associazione deve essere superiore all'efficacia di ciascun singolo componente (effetto additivo o di potenziamento)
- L'associazione deve minimizzare gli effetti umorali indesiderati
- L'associazione deve minimizzare gli eventi avversi