

PLACE

PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

9^a Edizione

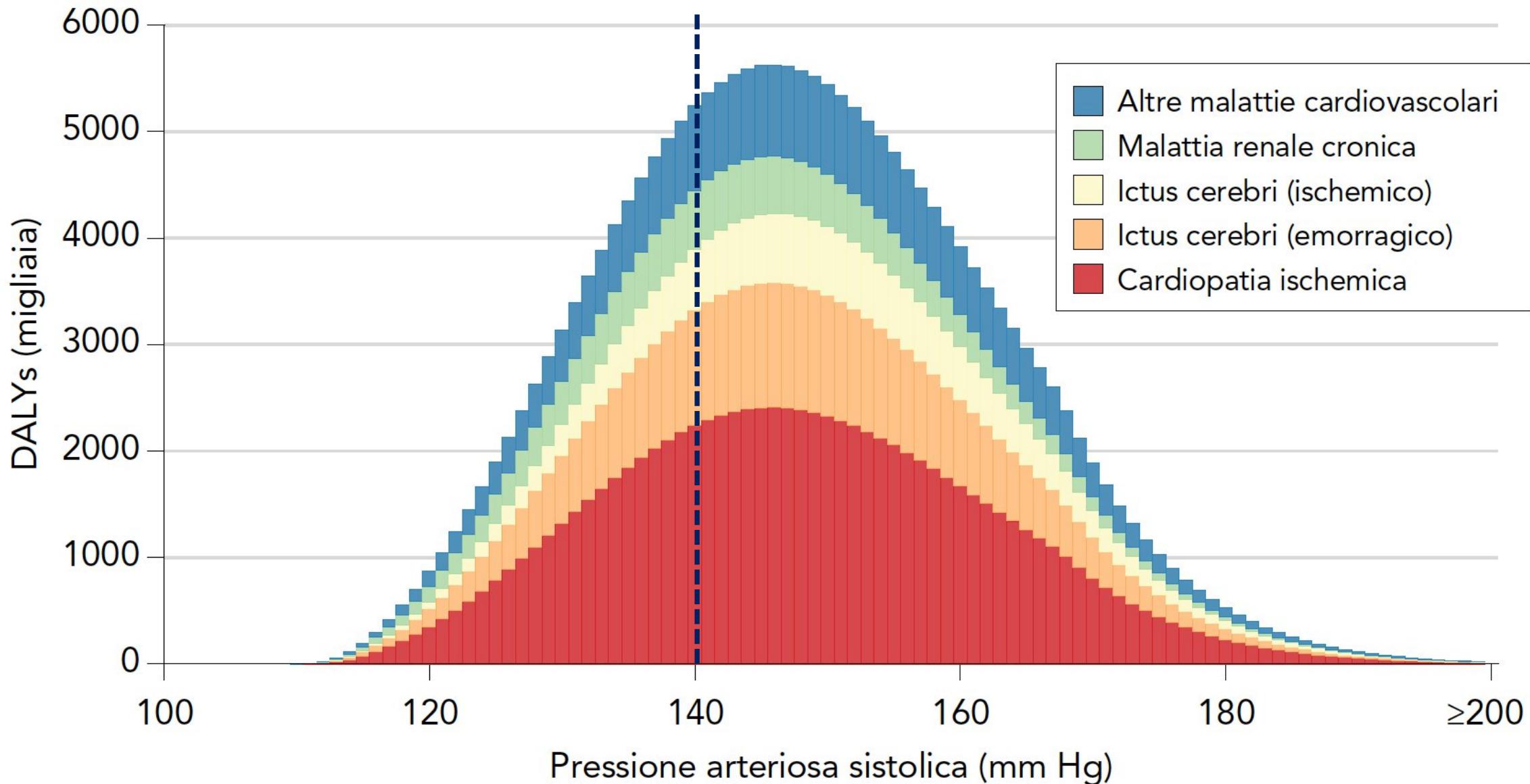
Medicina personalizzata e terapia antipertensiva: tra linee guida e “real-life”: quali farmaci e quali associazioni preferire?



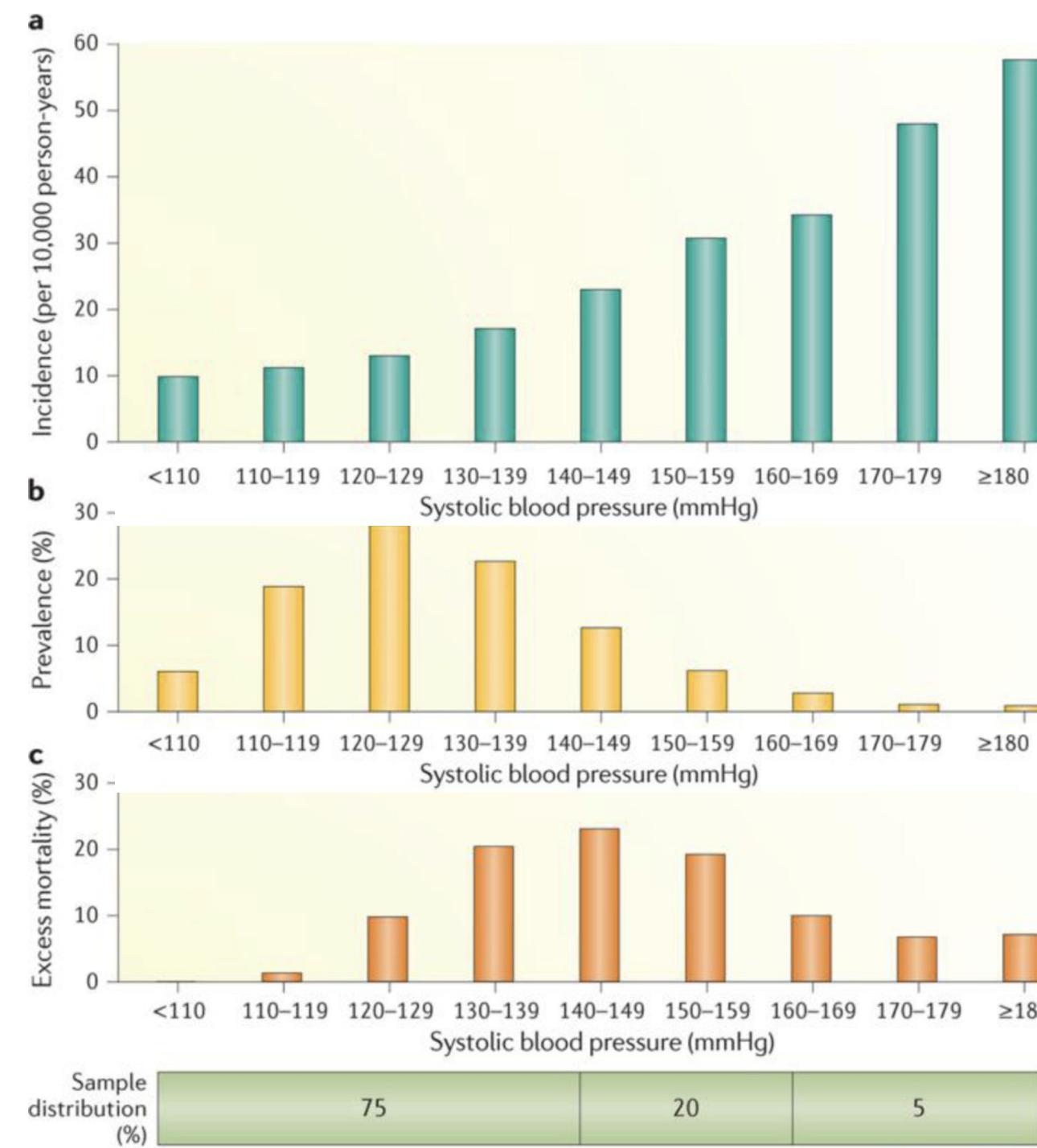
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Dipartimento MESVA
Università degli Studi di L'Aquila



Ipertensione Arteriosa come fattore di rischio cardiocerebrorenale



Hypertension



Relationship of systolic BP to subsequent risk of coronary heart disease mortality

Prevalence of coronary heart disease mortality

Estimation of the percent of excess coronary heart disease deaths occurring in each category of SBP



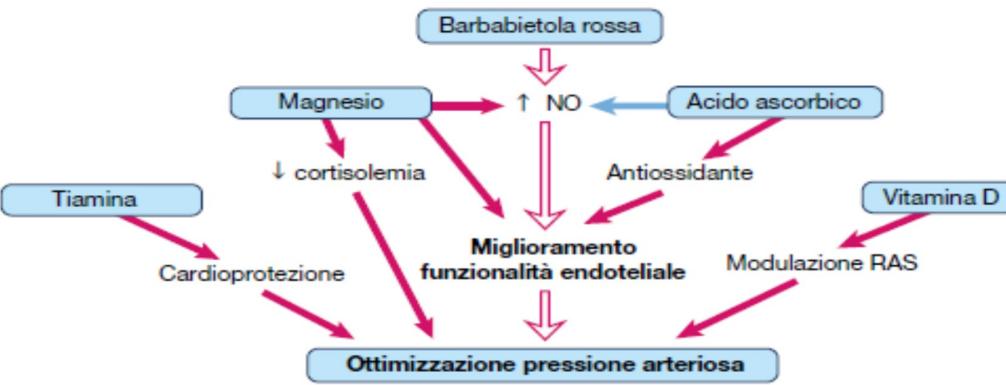
*"In an operational sense,
hypertension should be
defined in terms of a blood-
pressure level **above which**
investigation and
treatment do more good
than harm"*

... and so what about high-normal blood pressure management?

....These findings support the importance for worldwide cardiovascular risk of such a population of patients despite **no reliable evidence that may justify a drug-based therapeutic approach.**



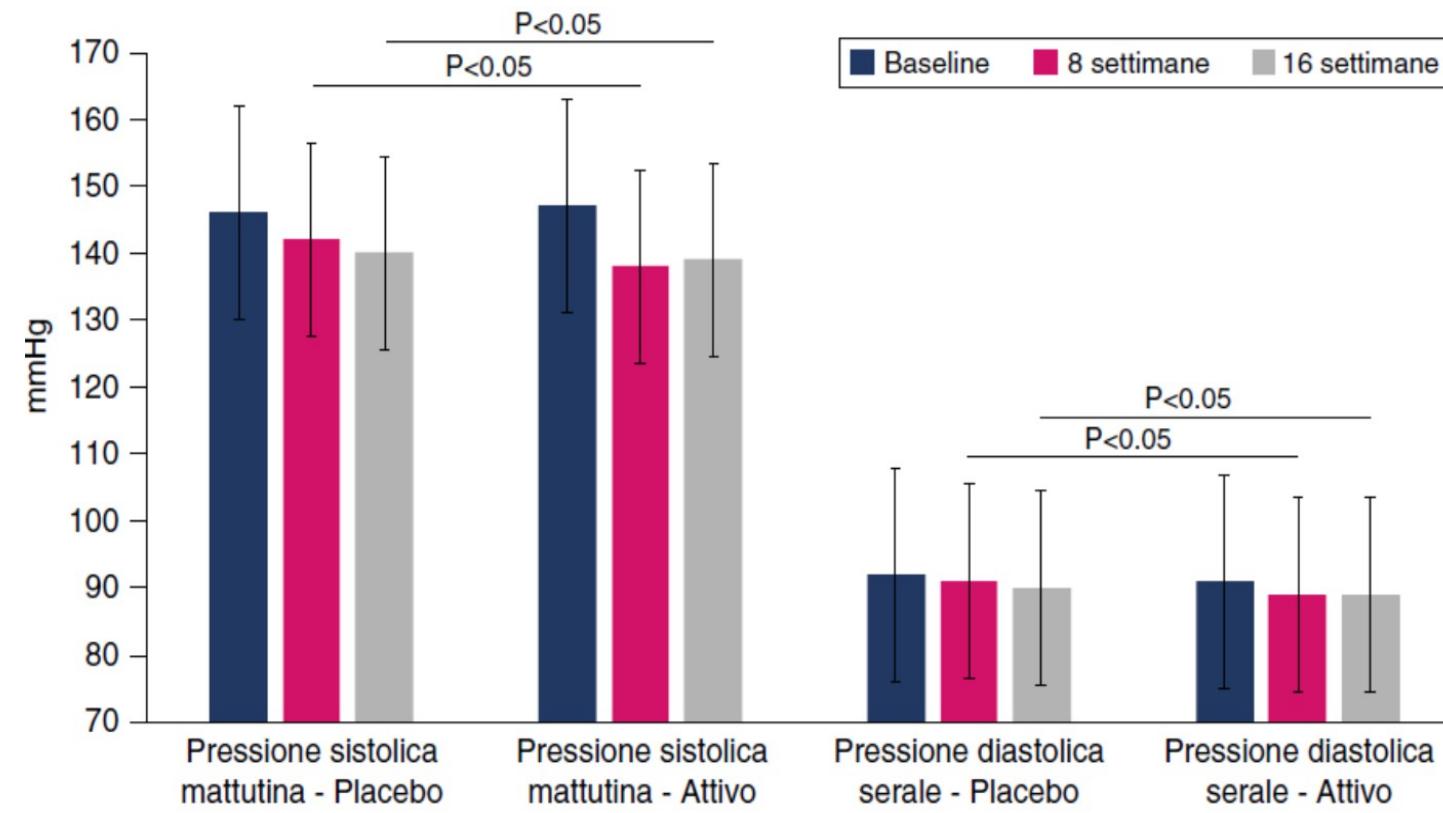
Effetto di un nutraceutico combinato sulla PA domiciliare mattutina e serale rispetto ai valori vasali e placebo



RISULTATI

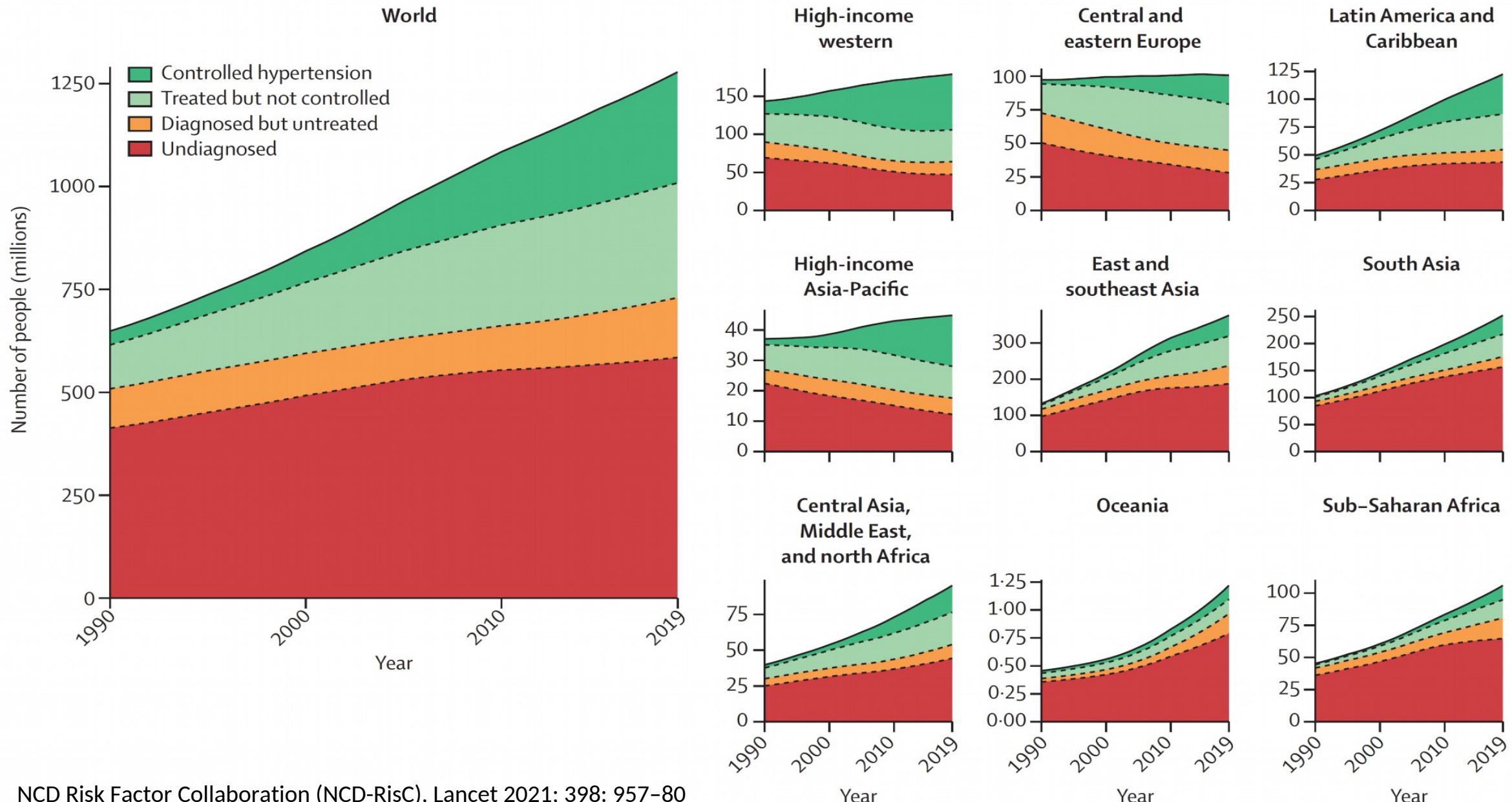
Effetti emodinamici ad 8/16 settimane:

- PA sistolica mattutina: **-2/-3 mmHg***
- PA diastolica mattutina: **-4/-5 mmHg***
- PA sistolica serale: **-2/-2 mmHg***



*Riduzione statisticamente significativa ($p<0.05$) sia rispetto al baseline sia rispetto al Placebo

Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants

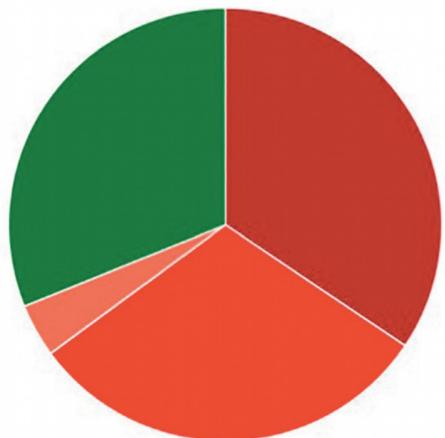


Bisogni attualmente insoddisfatti nell'iperteso ipercolesterolemico: i dati nazionali

ipercolesterolemici

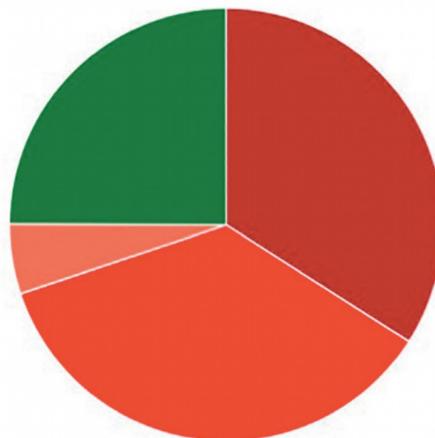
Ipercolesterolemici – Consapevolezza ed
adeguatezza del trattamento
Uomini – Italia

Periodo: 2008-2012 – Età: 35-74
Livello di istruzione: Tutti



Ipercolesterolemici – Consapevolezza ed
adeguatezza del trattamento
Donne – Italia

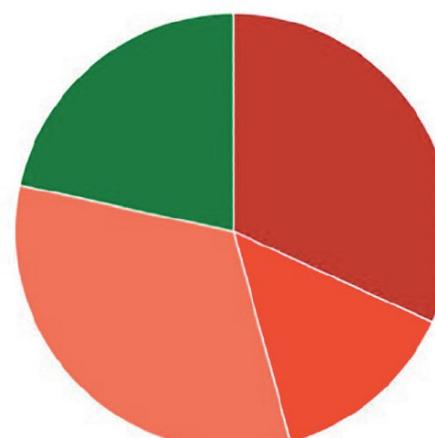
Periodo: 2008-2012 – Età: 35-74
Livello di istruzione: Tutti



ipertesi

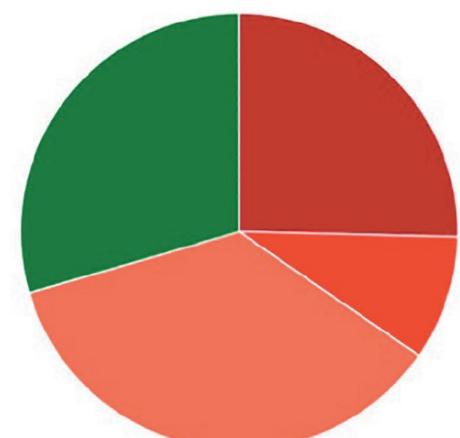
Ipertensione – Consapevolezza ed
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Ipertensione – Consapevolezza ed
adeguatezza del trattamento
Donne – Italia

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2013 ESH/ESC Guidelines for the management of arterial hypertension



Monotherapy can effectively reduce BP in only a limited number of hypertensive patients and that most patients require the combination of at least two drugs to achieve BP control.

Therefore, the issue is not whether combination therapy is useful, but whether it should always be preceded by an attempt to use monotherapy, **or whether—and when—combination therapy may be the initial approach.**

2018 ESC/ESH Guidelines for the management of arterial hypertension

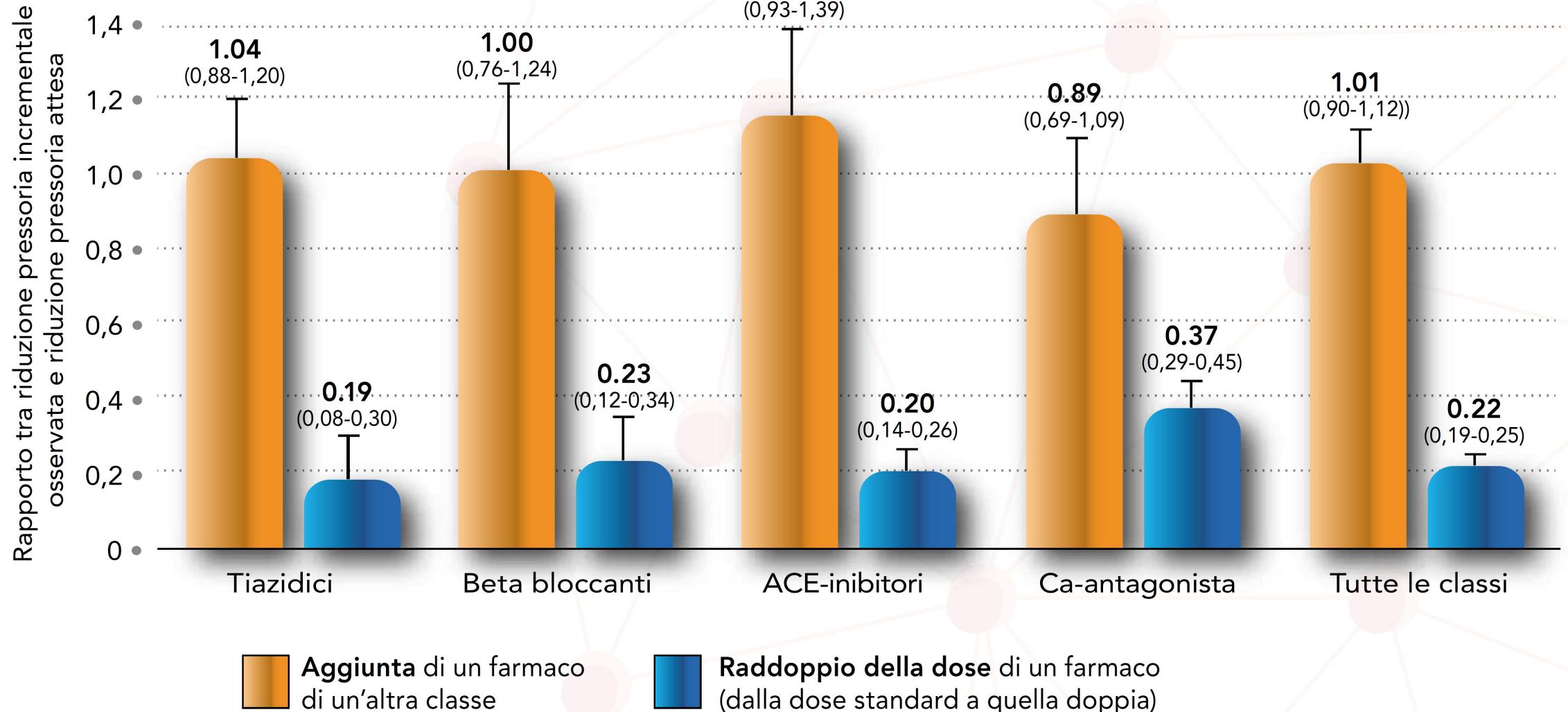
The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)

New concepts

A SPC treatment strategy to improve BP control

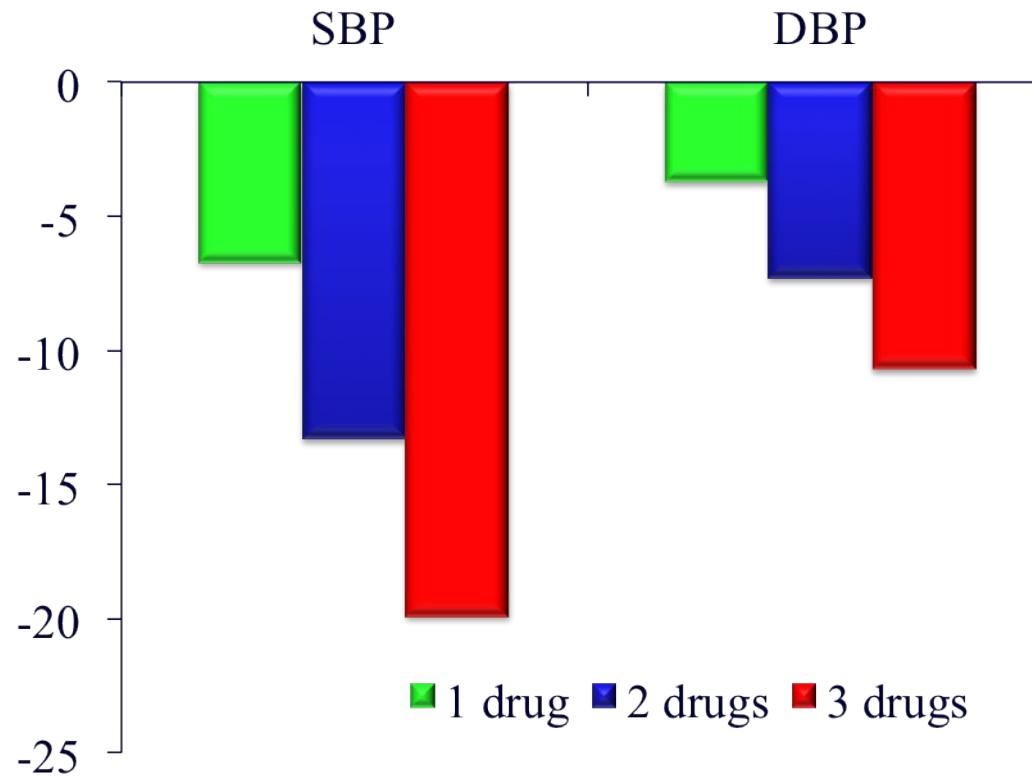
- Preferred use of **two-drug combination therapy** for the initial treatment of most people with hypertension.
- **A single-pill treatment strategy** for hypertension with the preferred use of SPC therapy for most patients.
- **Simplified drug treatment algorithms** with the preferred use of an ACE inhibitor or ARB, combined with a CCB and/or a thiazide/thiazide-like diuretic, as the core treatment strategy for most patients, with beta-blockers used for specific indications.

La riduzione pressoria incrementale che si ottiene combinando 2 classi di antipertensivi è 5 volte superiore a quello ottenibile raddoppiando la dose di un singolo farmaco

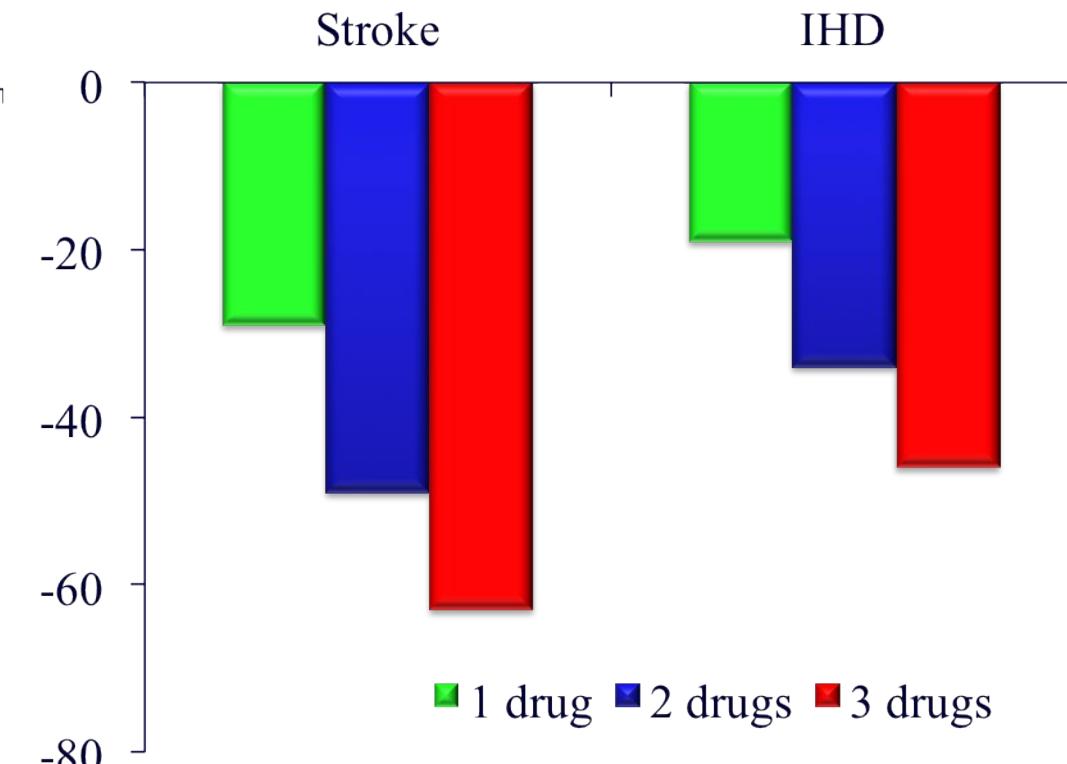


Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials

Efficacy: blood pressure lowering effects (mmHg) of drugs when used at half standard dose separately and in combination



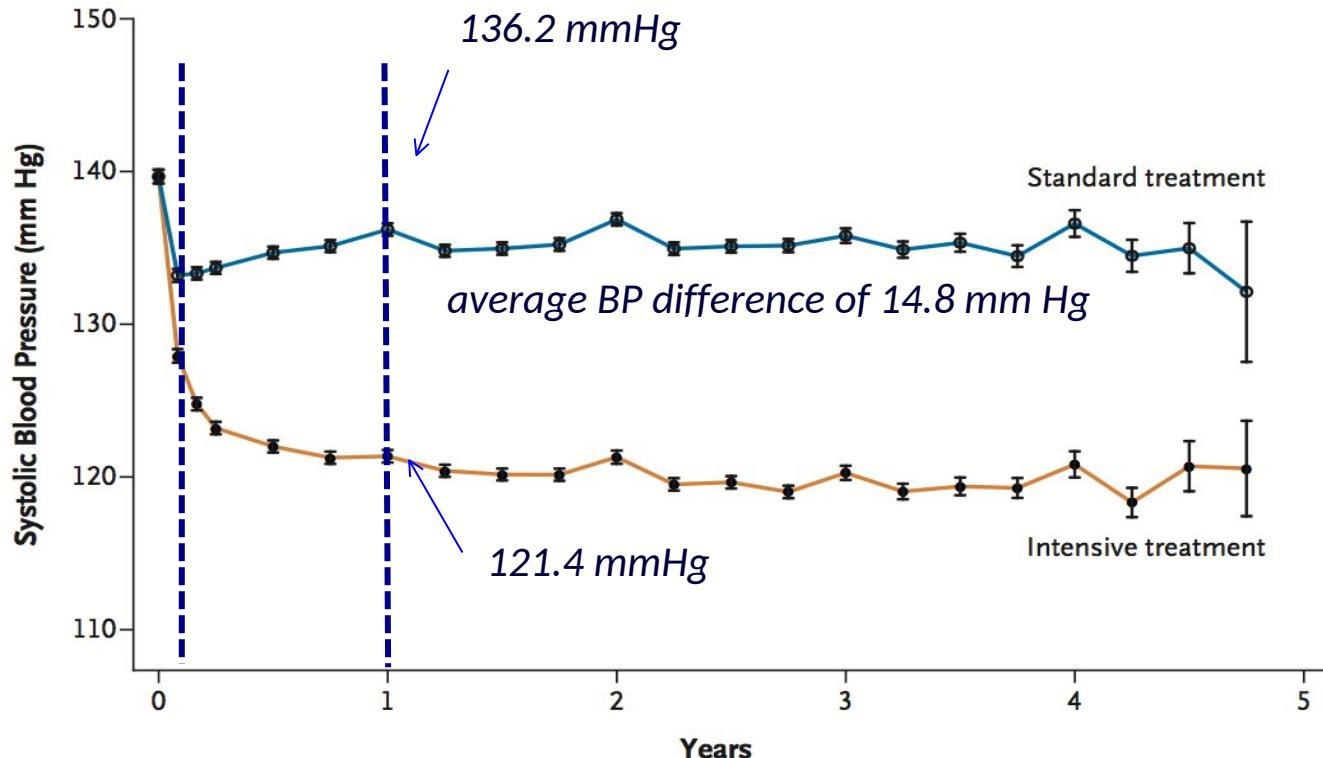
Reduction of the incidence of stroke and IHD events (%) when drugs are used separately and in combination at half standard dose



Systolic Blood Pressure in the Two Treatment Groups over the Course of the Trial: SPRINT

Number of agent	Intensive	Standard
1	10.5%	31.1%
2	30.5%	33.3%
3	31.8%	17.2%
4+	24.3%	6.9%

56% patients treated with ≥ 3 drugs



No. with Data

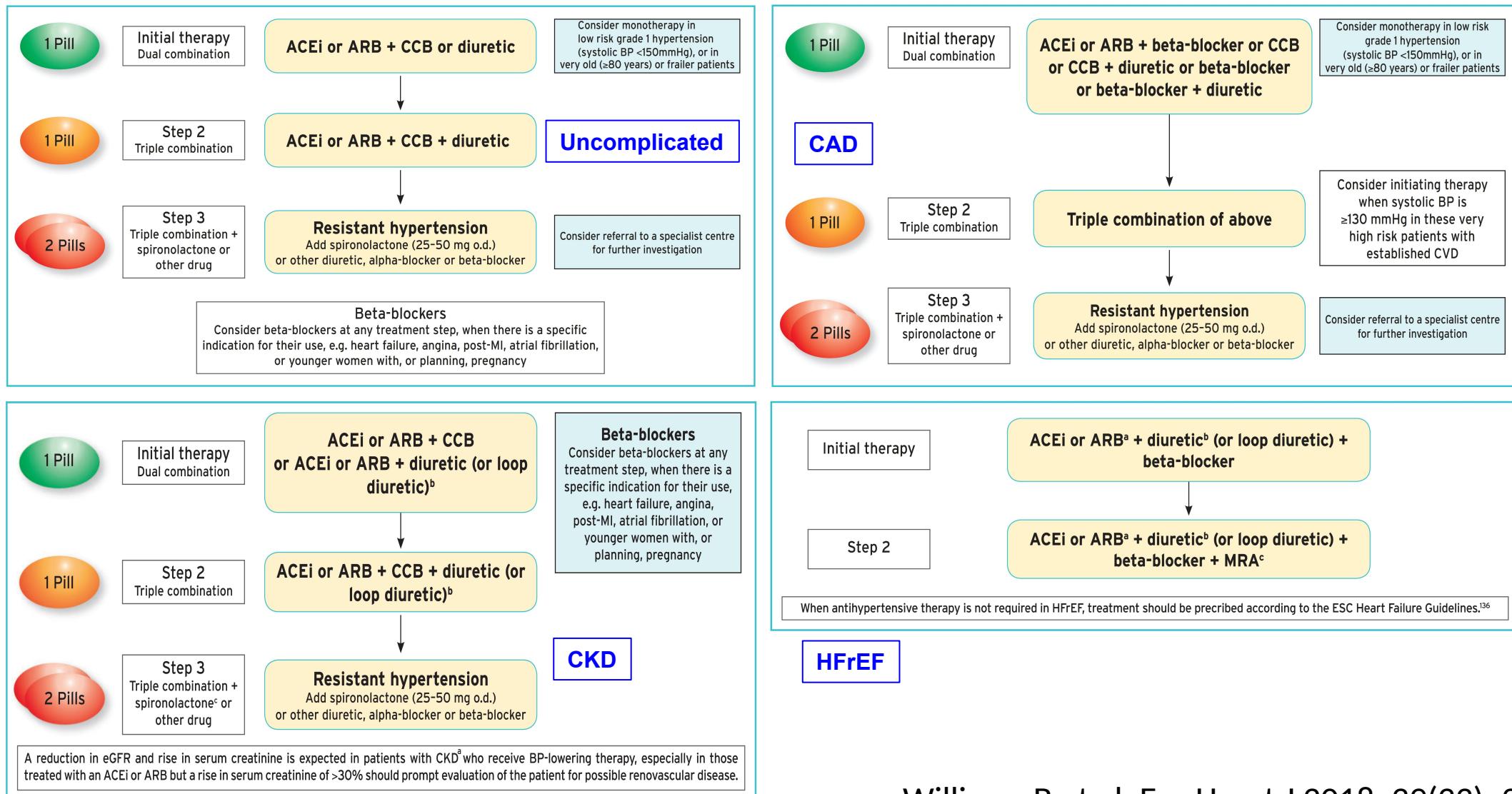
Standard treatment	4683	4345	4222	4092	3997	3904	3115	1974	1000	274
Intensive treatment	4678	4375	4231	4091	4029	3920	3204	2035	1048	286

Mean No. of Medications

Standard treatment	1.9	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.9
Intensive treatment	2.3	2.7	2.8	2.8	2.8	2.8	2.8	2.8	2.8	3.0

2018 ESC/ESH Guidelines for the management of arterial hypertension

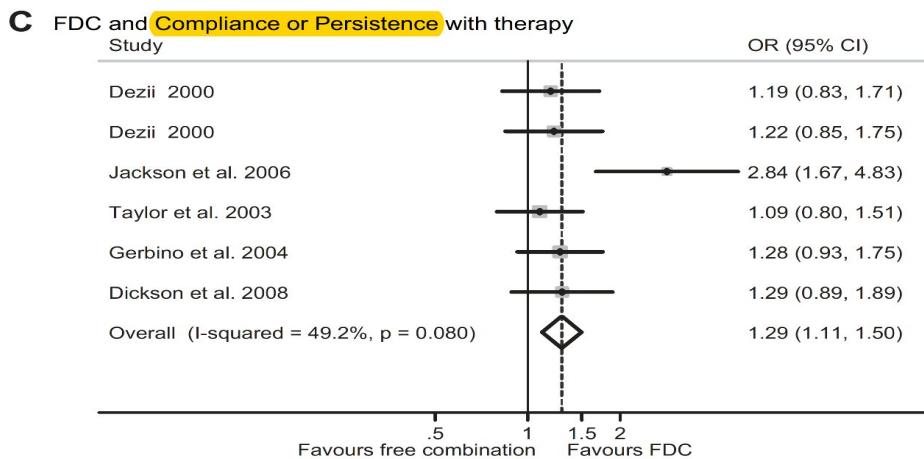
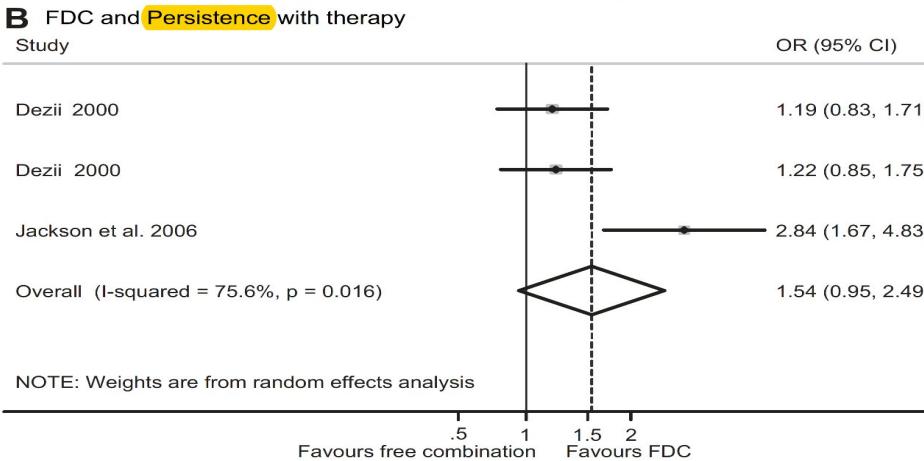
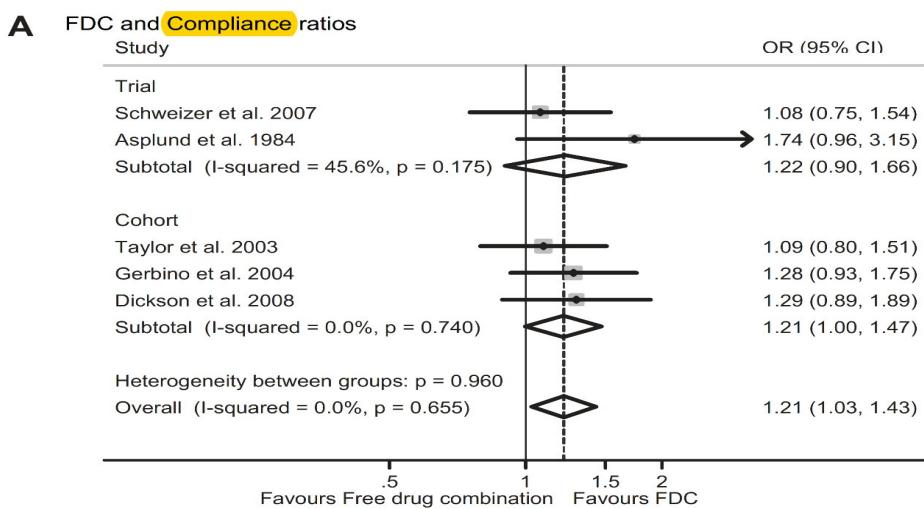
Drug treatment strategy for hypertension



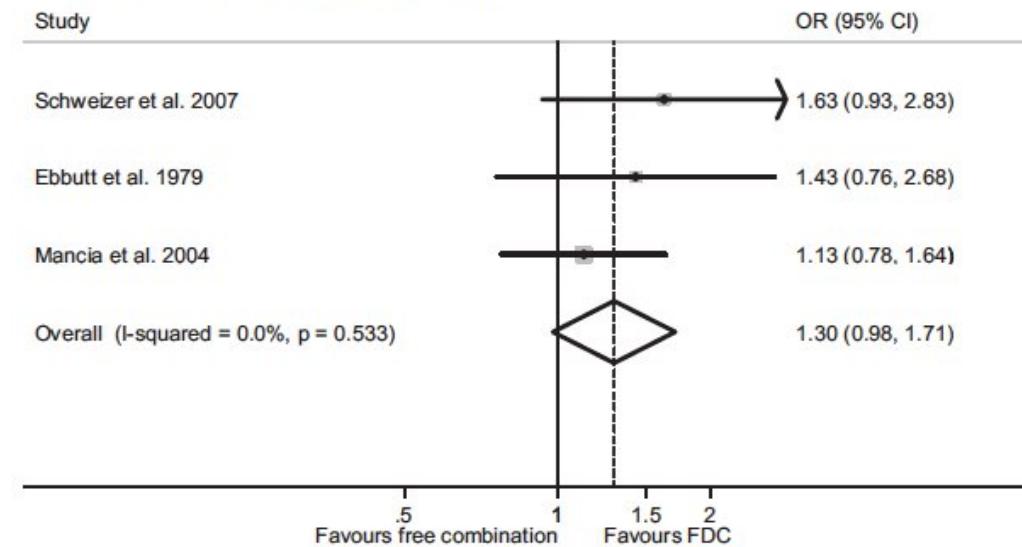
Antihypertensive Agents, Compliance

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

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



Systolic and Diastolic BP normalization ratios



...In conclusion, compared with three-drug combinations, FDCs of antihypertensive agents are associated with a significant improvement in compliance and with nonsignificant beneficial trends in BP and adverse effects.

Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET): a phase 3, randomised, double-blind, active-controlled trial



Clara K Chow, Emily R Atkins, Graham S Hillis, Mark R Nelson, Christopher M Reid, Markus P Schlaich, Peter Hay, Kris Rogers, Laurent Billot, Michael Burke, John Chalmers, Bruce Neal, Anushka Patel, Tim Usherwood, Ruth Webster, Anthony Rodgers, on behalf of the QUARTET Investigators

Summary

Background Treatment inertia is a recognised barrier to blood pressure control, and simpler, more effective treatment strategies are needed. We hypothesised that a hypertension management strategy starting with a single pill containing ultra-low-dose quadruple combination therapy would be more effective than a strategy of starting with monotherapy.

Lancet 2021; 398: 1043–52

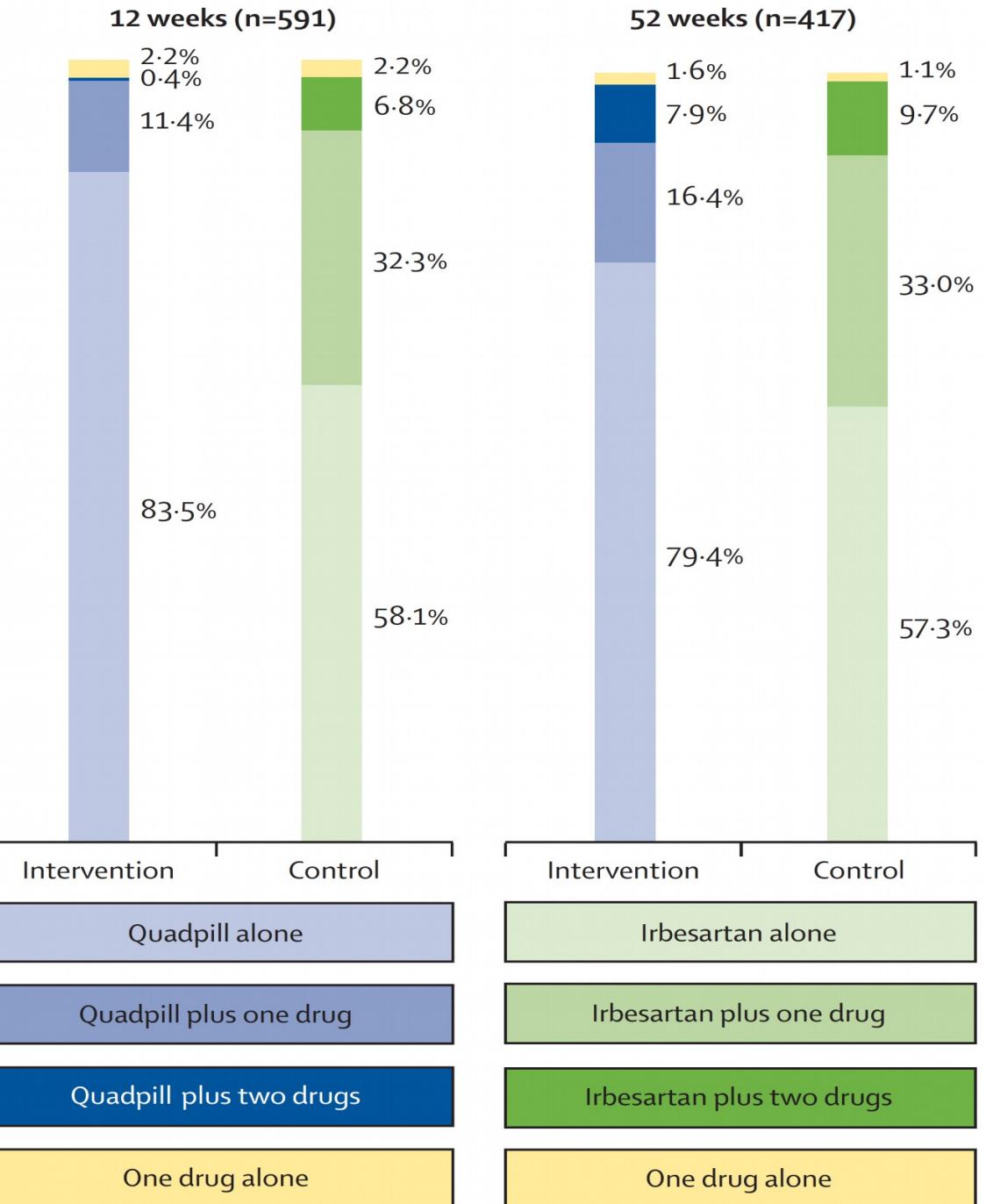
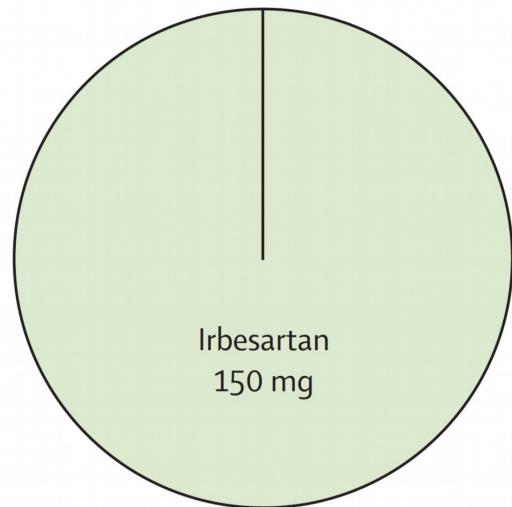
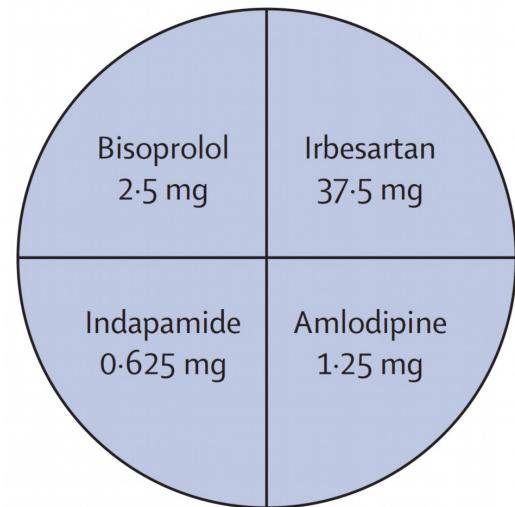
Published Online

August 29, 2021

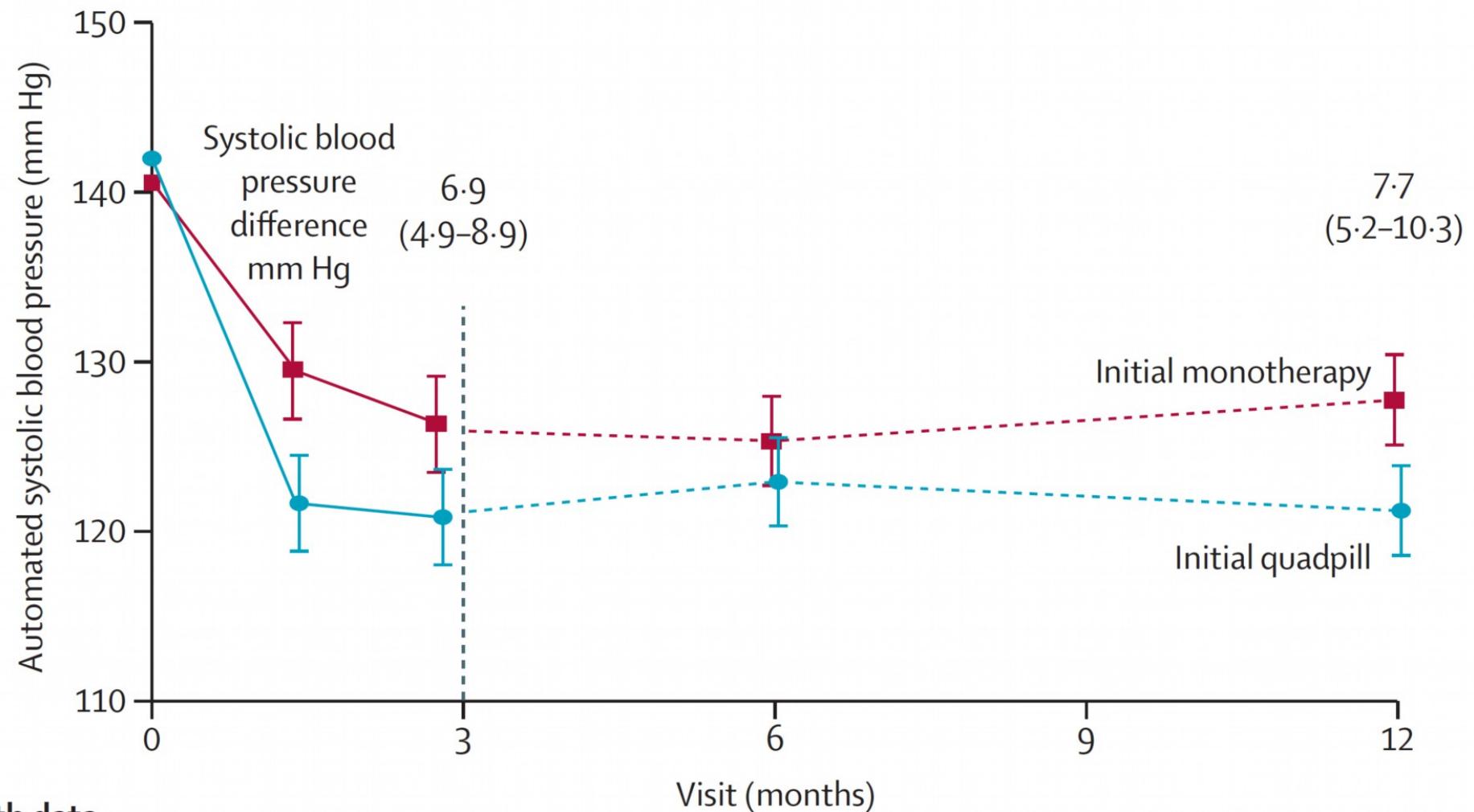
[https://doi.org/10.1016/S0140-6736\(21\)01922-X](https://doi.org/10.1016/S0140-6736(21)01922-X)

Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET): a phase 3, randomised, double-blind, active-controlled trial

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QUARTET trial: Mean systolic blood pressure to month 12, by group



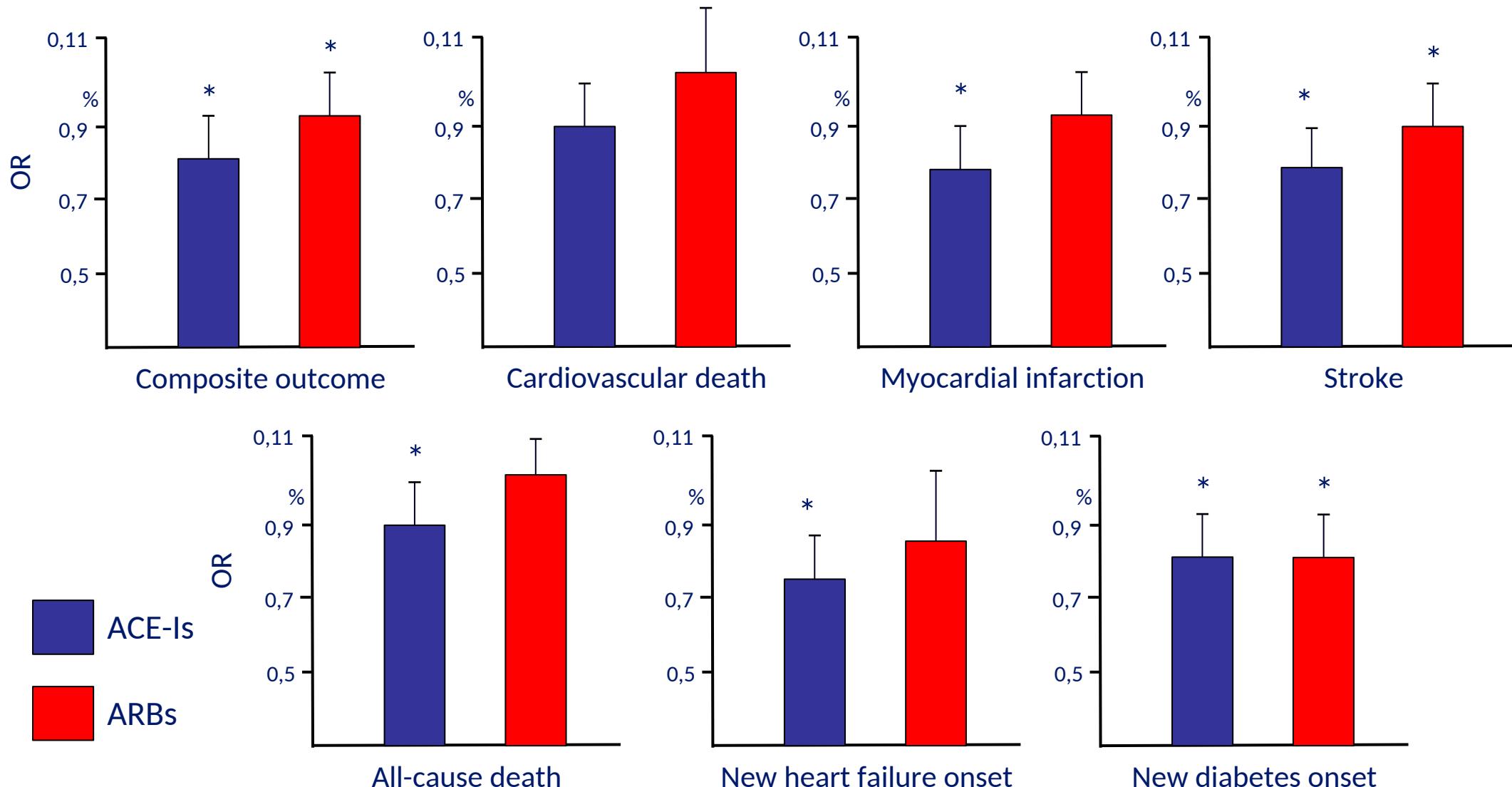
Number with data

Initial quadpill	300	276	267	192	178
Initial monotherapy	291	272	270	188	180

2018 ESC/ESH Guidelines for the management of uncomplicated arterial hypertension

ESH/ESC 2018 Recommendations	Class	Level
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	I	A

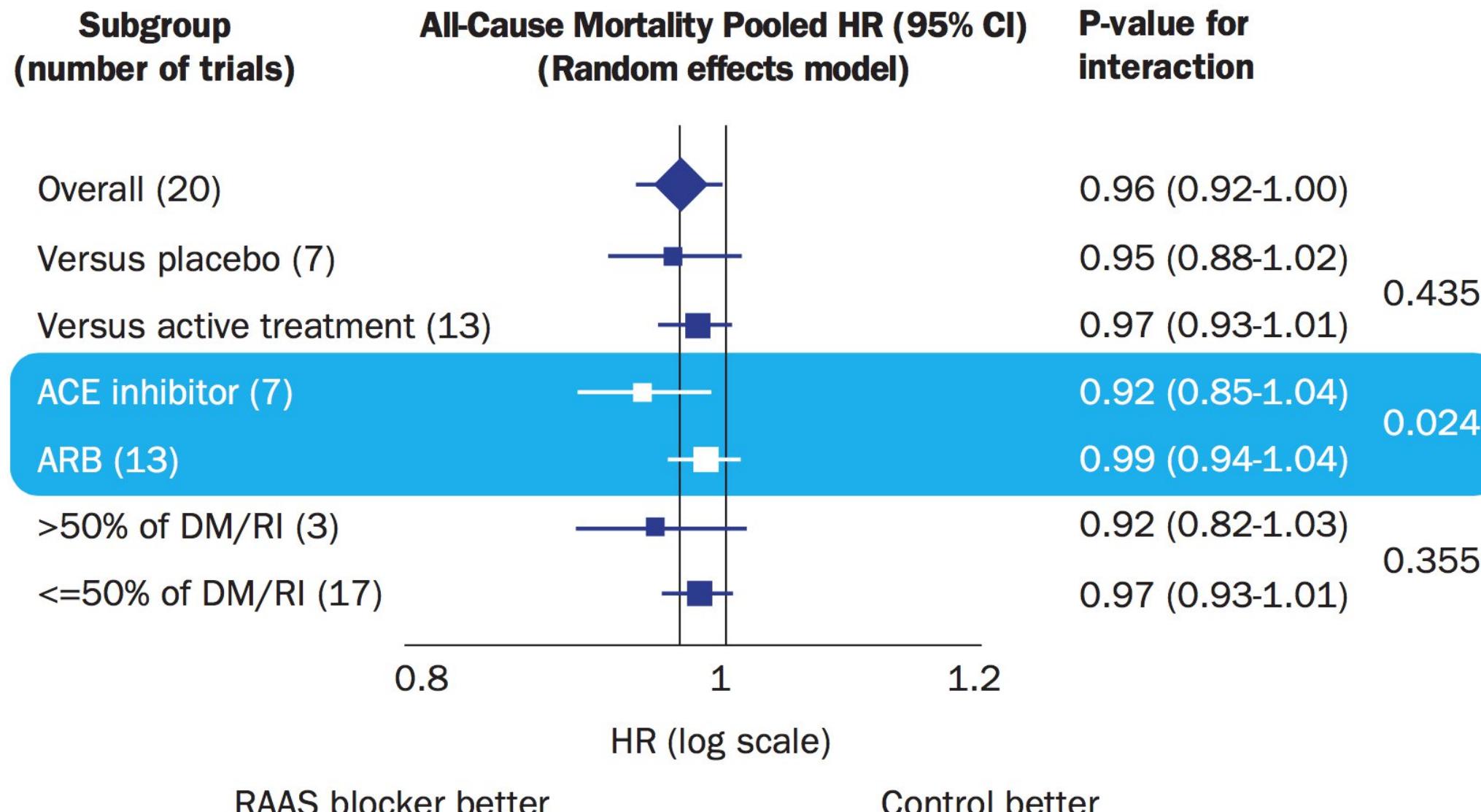
Effect of ACE-Is or ARBs on outcomes in 108,212 high risk patients



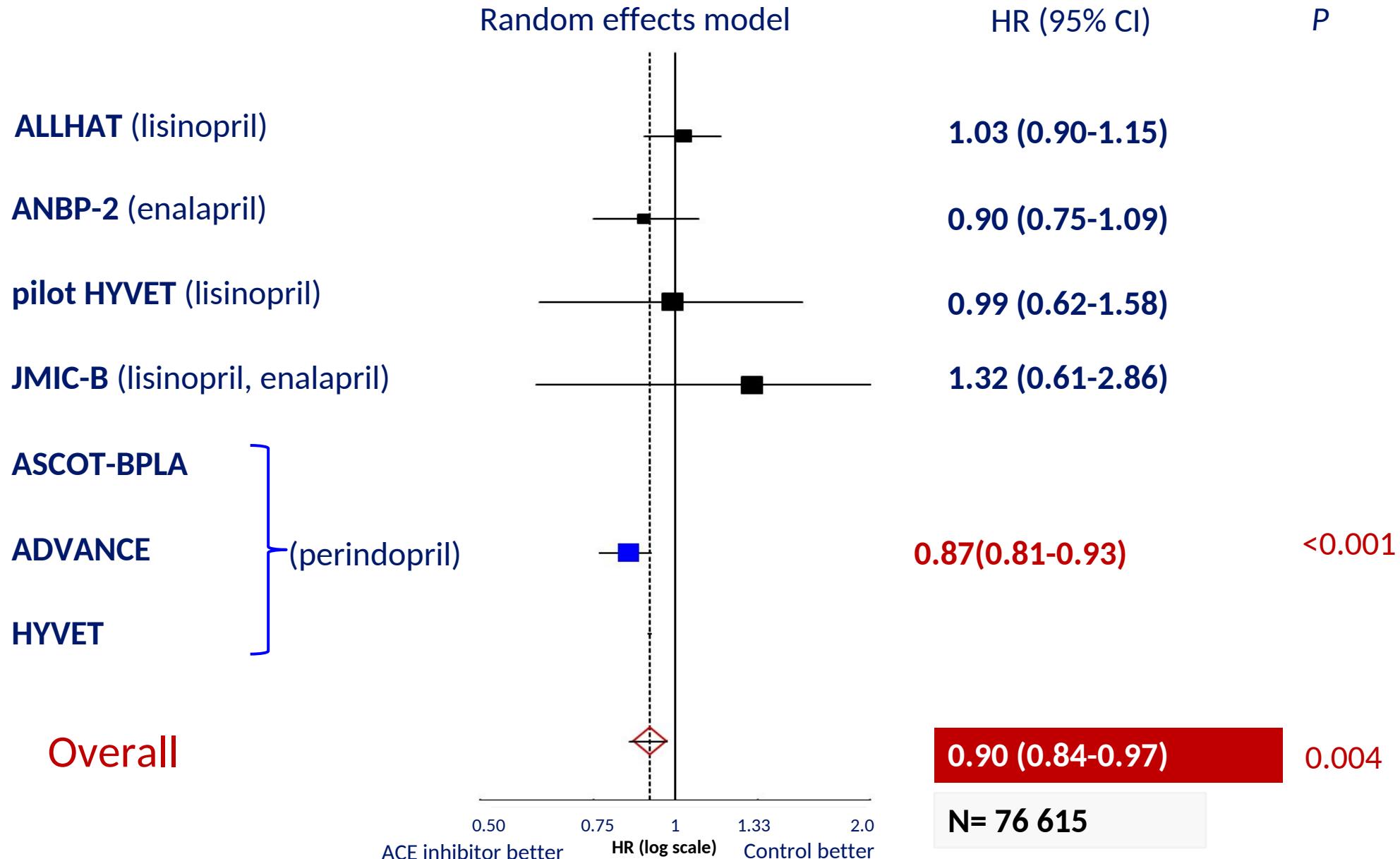
* outcome significantly reduced as compared to placebo

Savarese G et al, JACC 2013

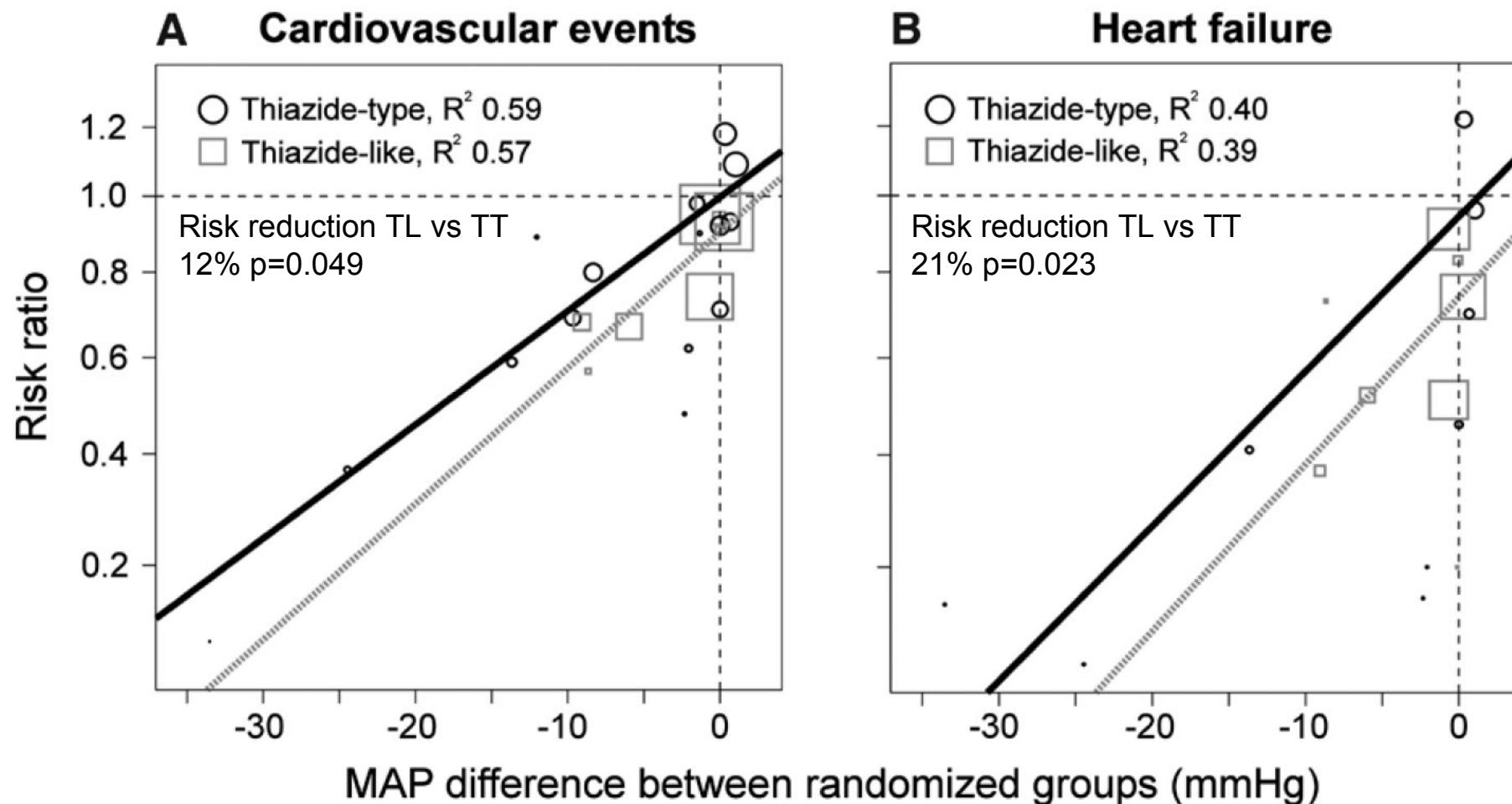
ACE inhibitors reduce mortality in hypertension: a meta-analysis of RCT of (RAAS) inhibitors involving 158,998 patients.



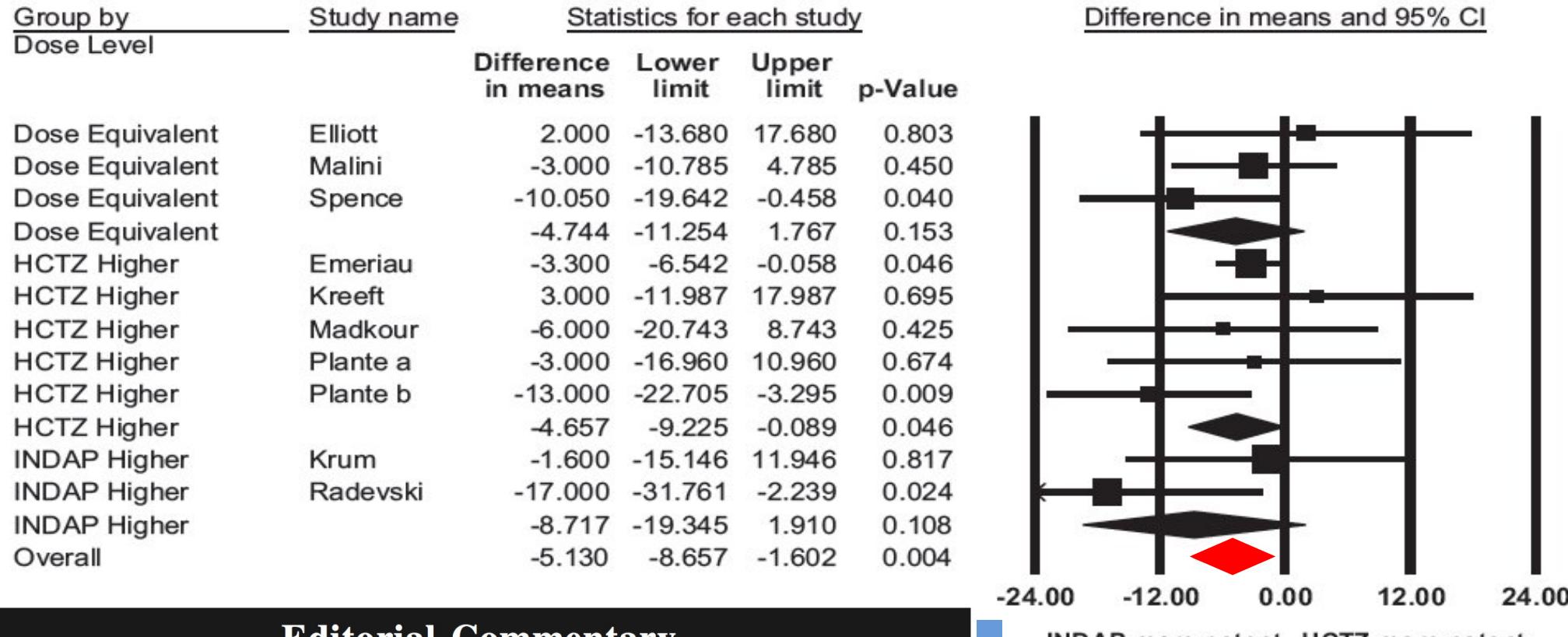
All-cause mortality: effect of ACE inhibitors



Relationship between the risk ratio of CVE and HF and the BP difference between treatment and control in patients treated with **thiazide-type** and **thiazide-like** diuretics



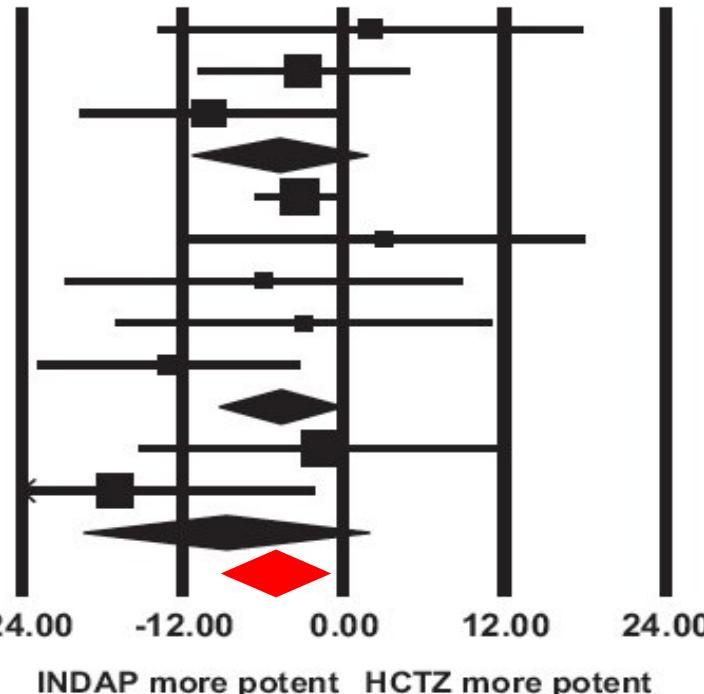
Metaanalysis comparing hydrochlorothiazide (HCTZ) and indapamide (INDAP) in patients with HTN: effect of BP



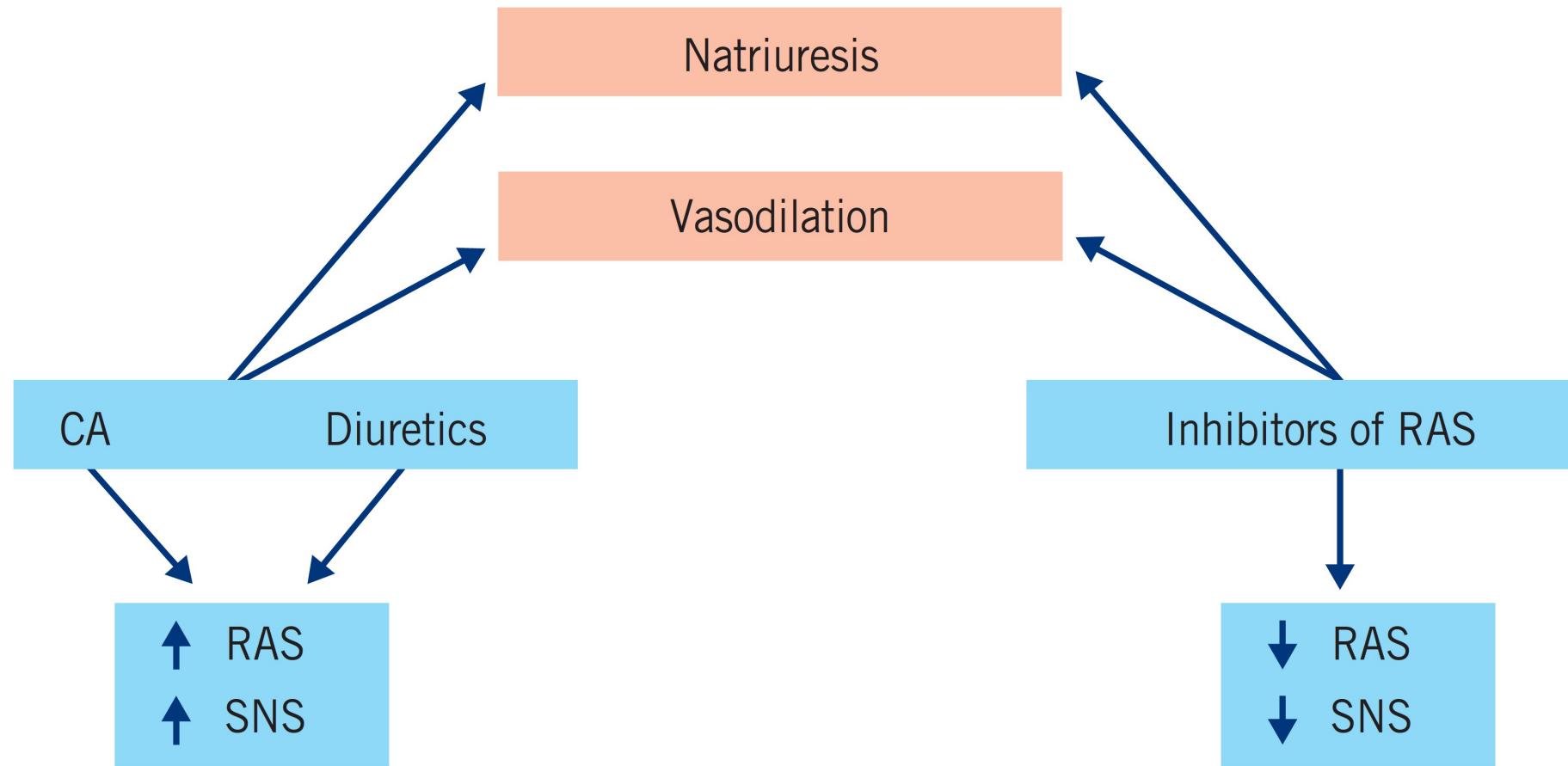
Editorial Commentary

Indapamide
Is It The Better Diuretic for Hypertension?

Norman M. Kaplan



Reciprocal action mechanism of inhibitors of angiotensin renin system diuretics and calcium channel blockers



CA: Calcium channel blockers; RAS: Renin angiotensin system; SNS: Sympathetic nervous system

Non rational (or homeopathic) combinations of antihypertensive drugs

Combination of drugs **without additive BP lowering effect**

- Diuretic + Ca-antagonist
- b-blocker + ACE-inhibitor (or AT1-antagonist)
- ACE-inhibitor + AT1-antagonist

Combination of drugs with **negative interaction on BP lowering effect**

- ✓ α_1 -antagonist + clonidine



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)

Gaps in the evidence and need for further studies

Impact of single-pill vs. multidrug treatment strategies on

- ❖ adherence to treatment,
- ❖ BP control, and
- ❖ clinical outcomes.

New concepts

Detecting poor adherence to drug therapy

- A strong emphasis on the importance of evaluating treatment adherence as a major cause of poor BP control.



L'uso dei Farmaci in Italia

Rapporto Nazionale
Anno 2019



Aderenza e persistenza al trattamento con farmaci antipertensivi

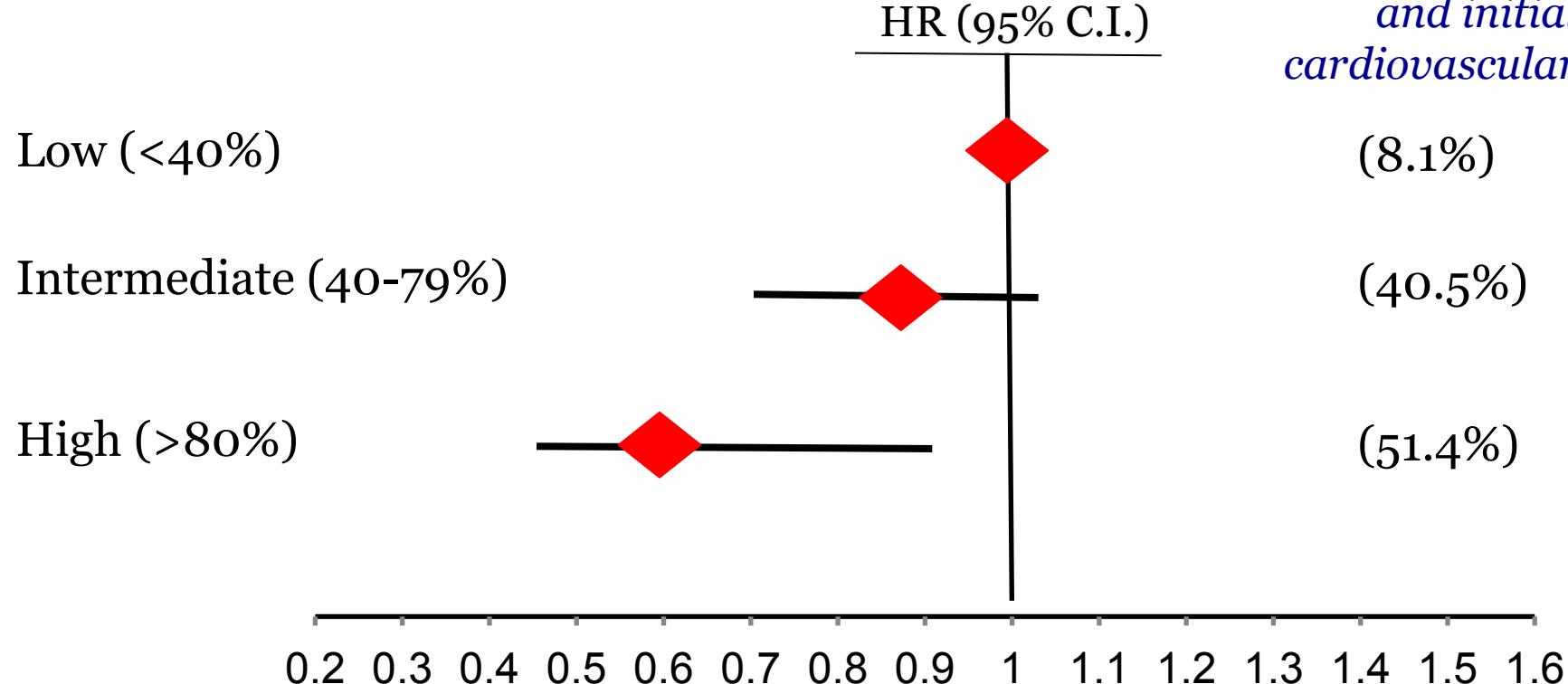
	Totale N=266.457	Nord N=119.719	Centro N=54.262	Sud N=92.476
Bassa aderenza al trattamento con antipertensivi (%)*†				
45-54 anni	16,4	15,1	16,6	17,6
55-64 anni	16,1	15,0	16,0	17,4
65-74 anni	17,7	16,7	17,5	19,2
75-84 anni	20,2	18,8	20,8	22,2
≥ 85 anni	25,0	22,8	25,7	28,2
Donne	20,5	19,1	20,8	22,1
Uomini	14,7	13,9	14,7	15,8
Totale	17,7	16,6	18,0	19,1
Alta aderenza al trattamento con antipertensivi (%)*†				
45-54 anni	54,8	56,7	55,8	52,3
55-64 anni	55,4	56,5	56,7	53,5
65-74 anni	53,9	54,6	55,9	51,8
75-84 anni	49,5	50,6	50,0	47,3
≥ 85 anni	41,0	42,1	41,2	39,0
Donne	48,7	49,9	49,5	46,7
Uomini	58,0	58,7	59,5	56,2
Totale	53,1	54,1	54,1	51,2

Persistenza (%) 3 mesi 6 mesi 12 mesi

Uomini	71,6	59,1	48,9
Donne	77,8	66,7	57,5

Adherence to Antihypertensive Medications and CV Morbidity Among Newly Diagnosed Hypertensive Patients

Adherence to AHT (6 months) and CV events (PDC)



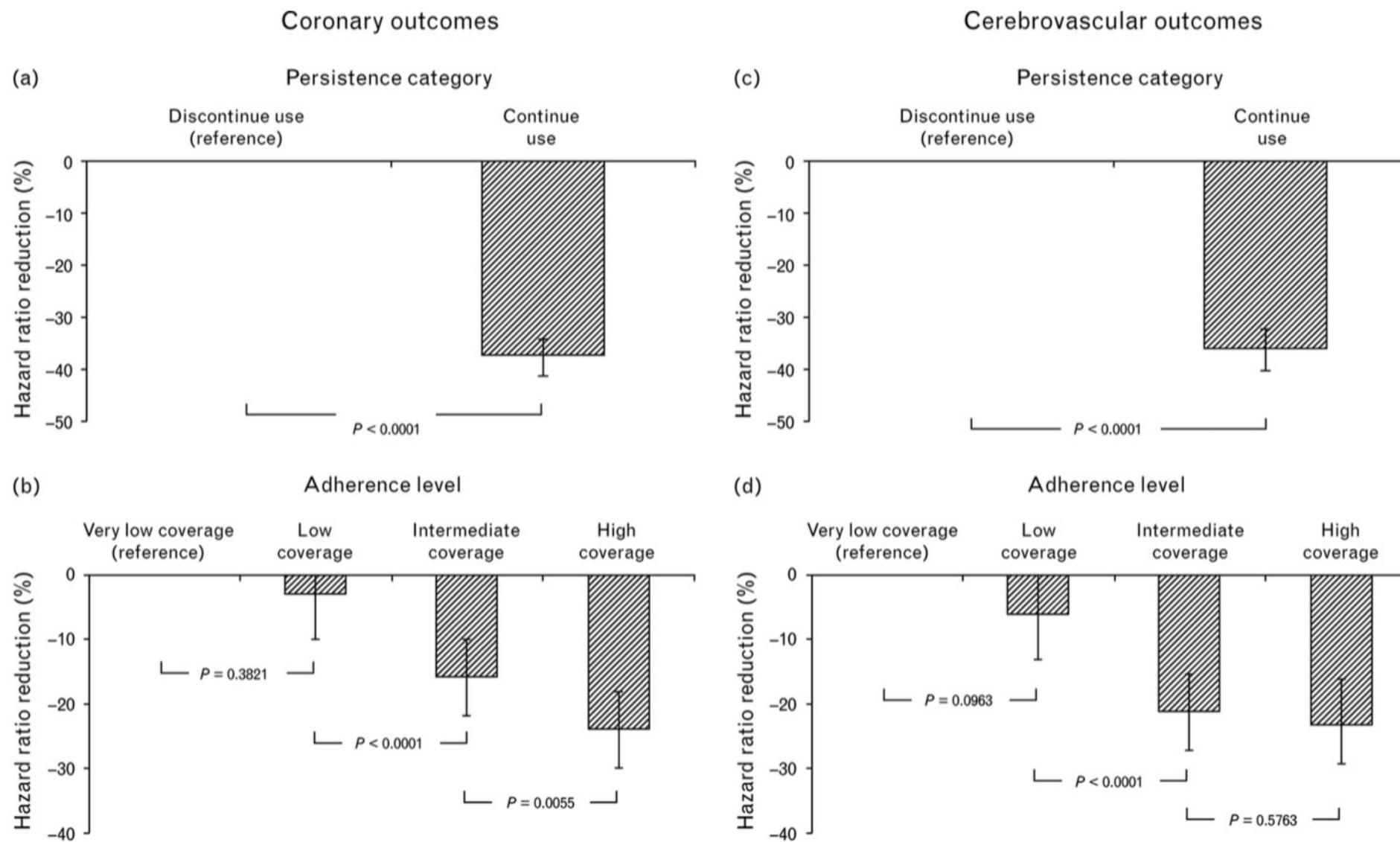
*18 806 newly diagnosed
hypertensives, newly
treated for hypertension
and initially free of
cardiovascular diseases*

(8.1%)

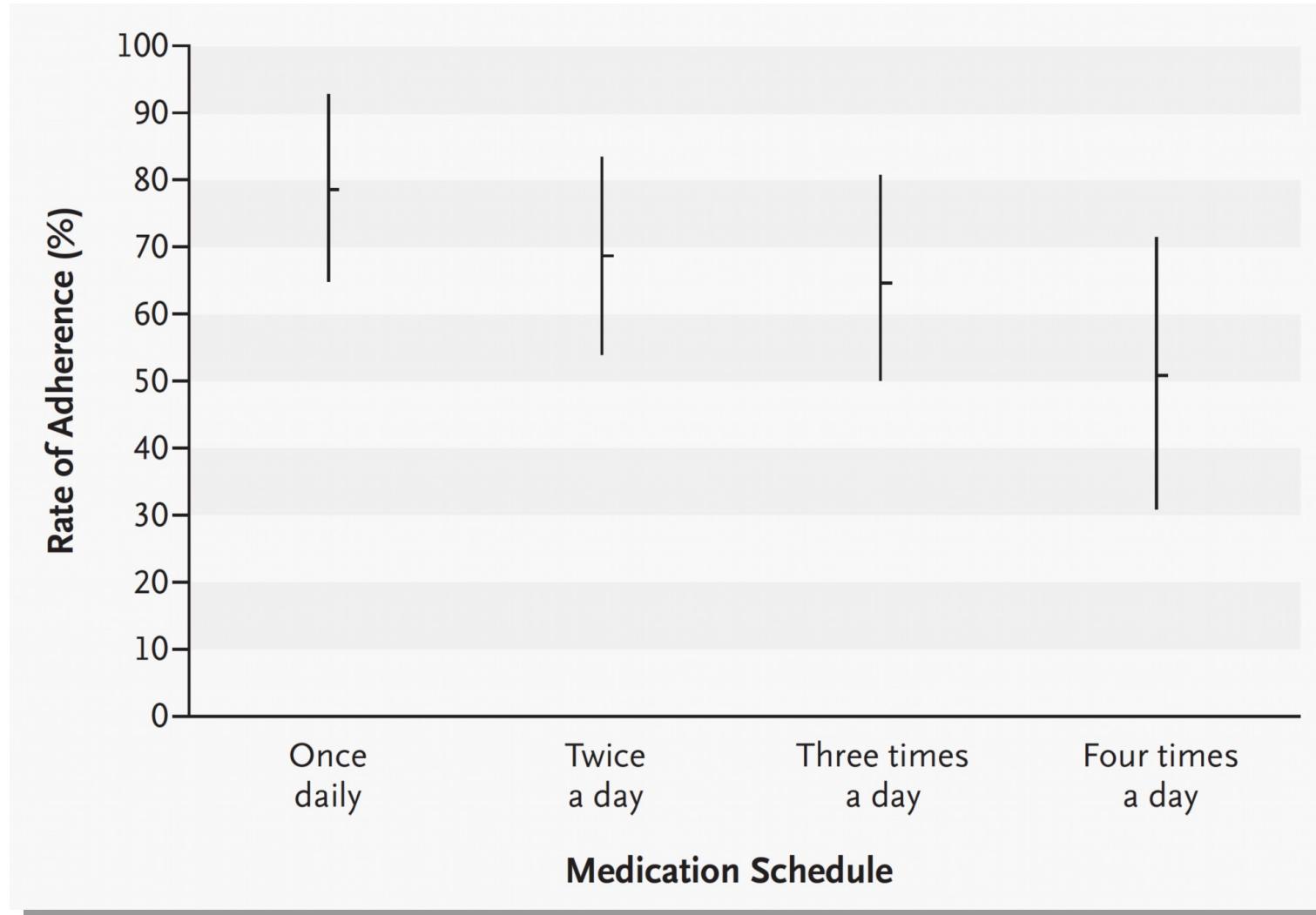
(40.5%)

(51.4%)

Effects of Persistence or Adherence with Antihypertensive Drug Therapy on the Reduction in Hazard Ratio† of Coronary (n = 6665) and Cerebrovascular (n = 5351) Outcomes in 242,594 Patients



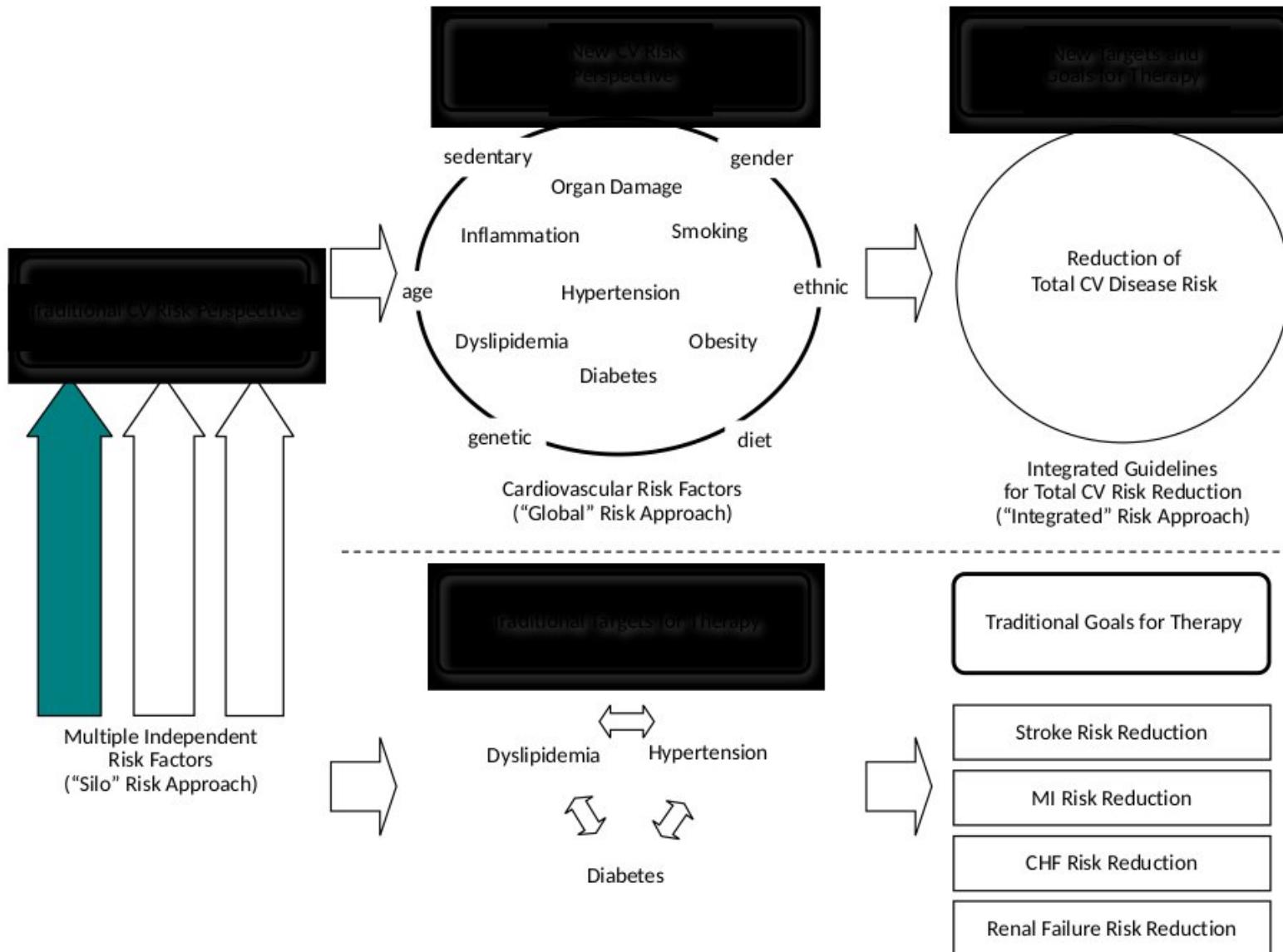
Adherence to Medication According to Frequency of Doses



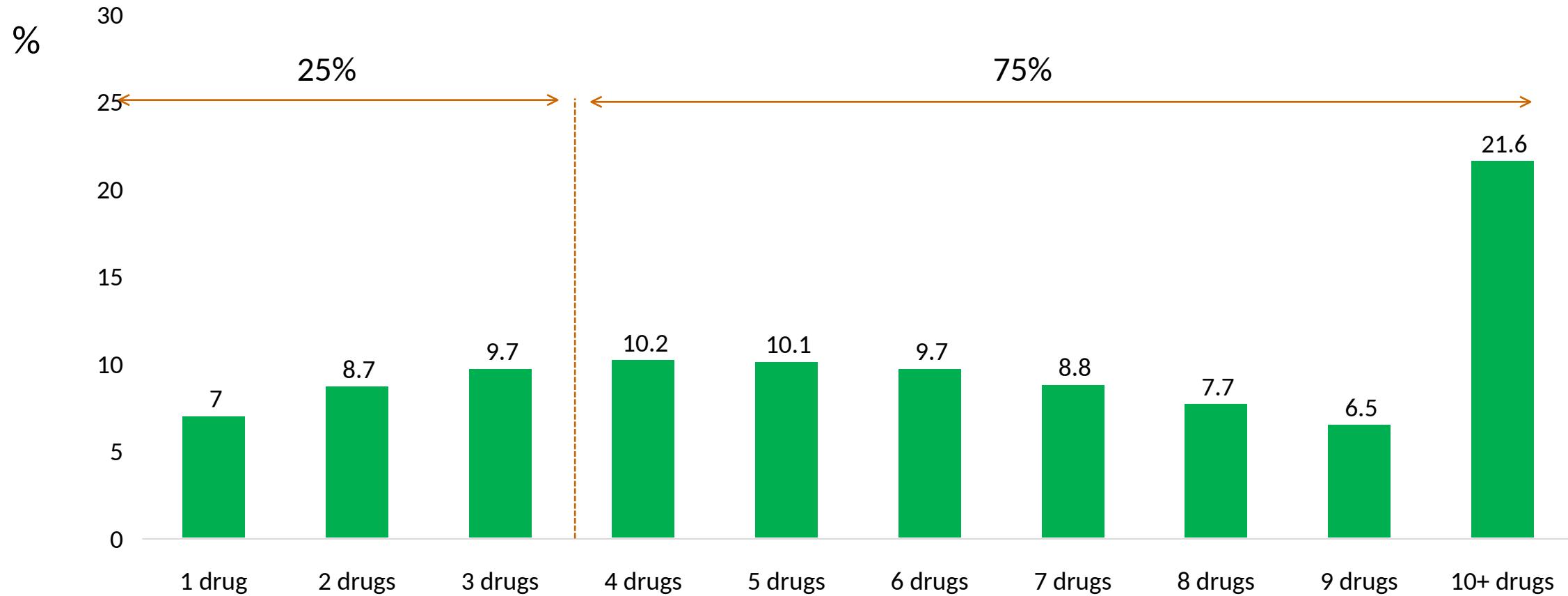
Drugs don't work in patients
who don't take them

— C. Everett Koop, M.D.

Total Cardiovascular Risk Assessment



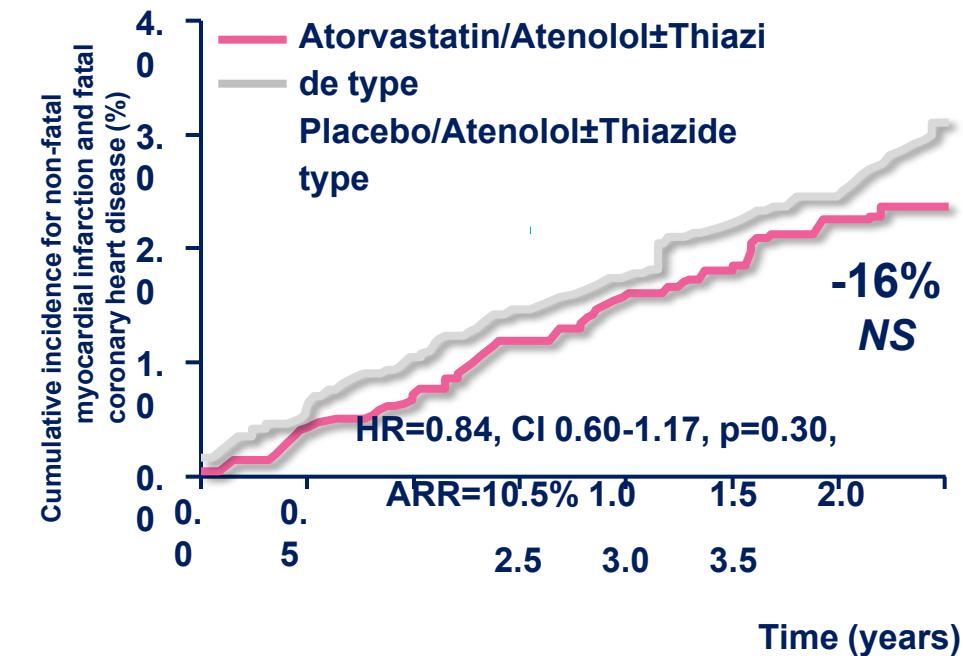
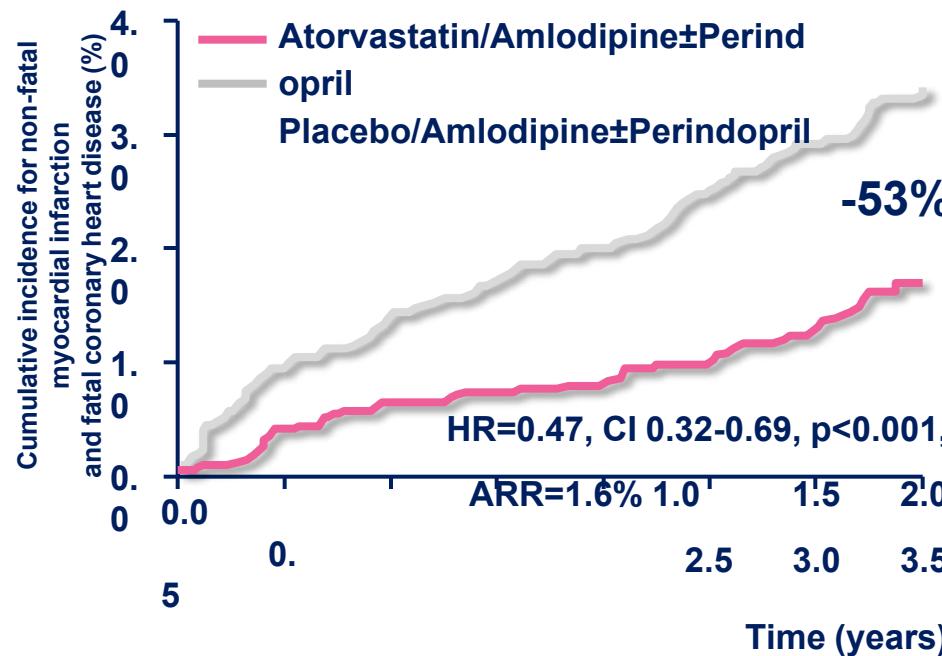
Distribution of drug consumers among subjects aged >65 years by number of different drugs



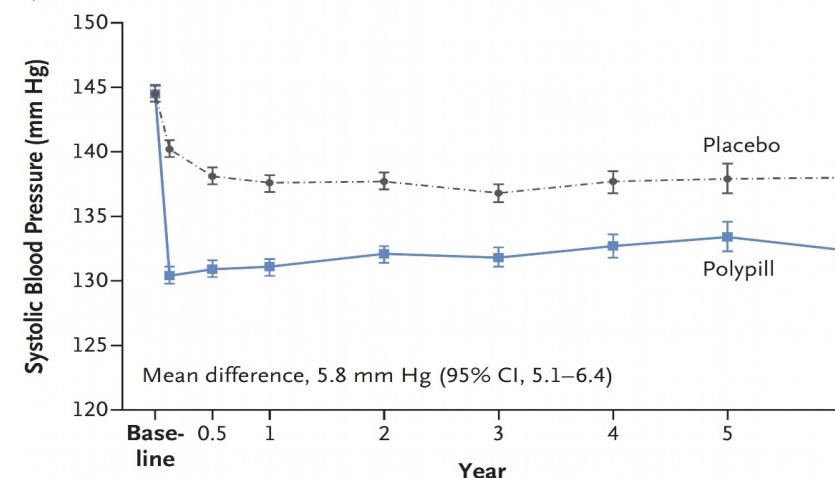
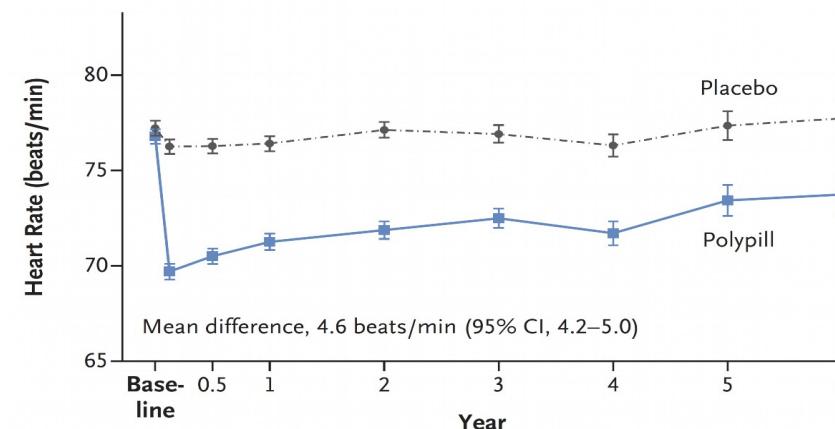
Synergy between atorvastatin, amlodipine and perindopril for cardiovascular protection

ASCOT-LLA, RCT

n=10,305 hypertensive patients with at least 3 cardiovascular risk factors and total cholesterol ≤6.5 mmol/L. Follow-up 3.3 years

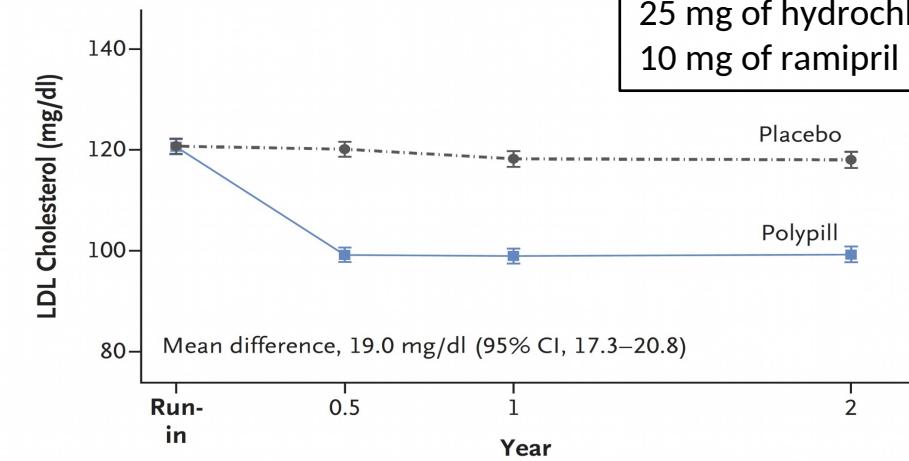


"The more likely basis for the proposed synergy is supported by the observation that significant benefits of atorvastatin were seen in the amlodipine/perindopril-based treatment limb within 3 months of assignment to treatment"

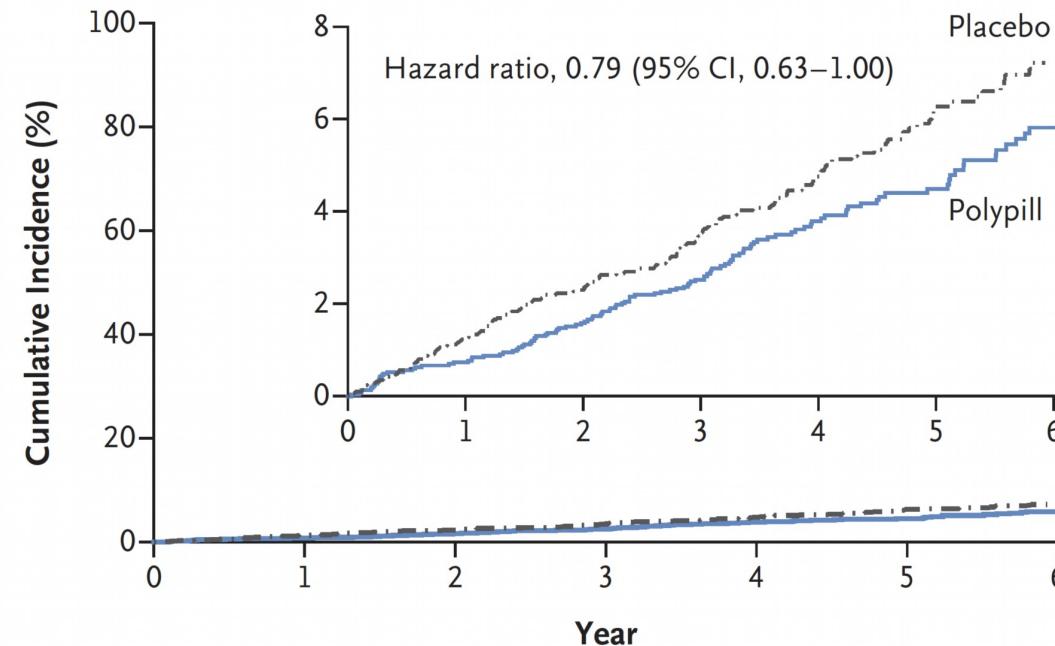
A Systolic Blood Pressure**B Heart Rate**

Polypill with or without Aspirin in Persons without Cardiovascular Disease

S. Yusuf, P. Joseph, A. Dans, P. Gao, K. Teo, D. Xavier, P. López-Jaramillo, K. Yusoff, A. Santoso, H. Gamra, S. Talukder, C. Christou, P. Girish, K. Yeates, F. Xavier, G. Dagenais, C. Rocha, T. McCready, J. Tyrwhitt, J. Bosch, and P. Pais, for the International Polycap Study 3 Investigators*

C LDL Cholesterol

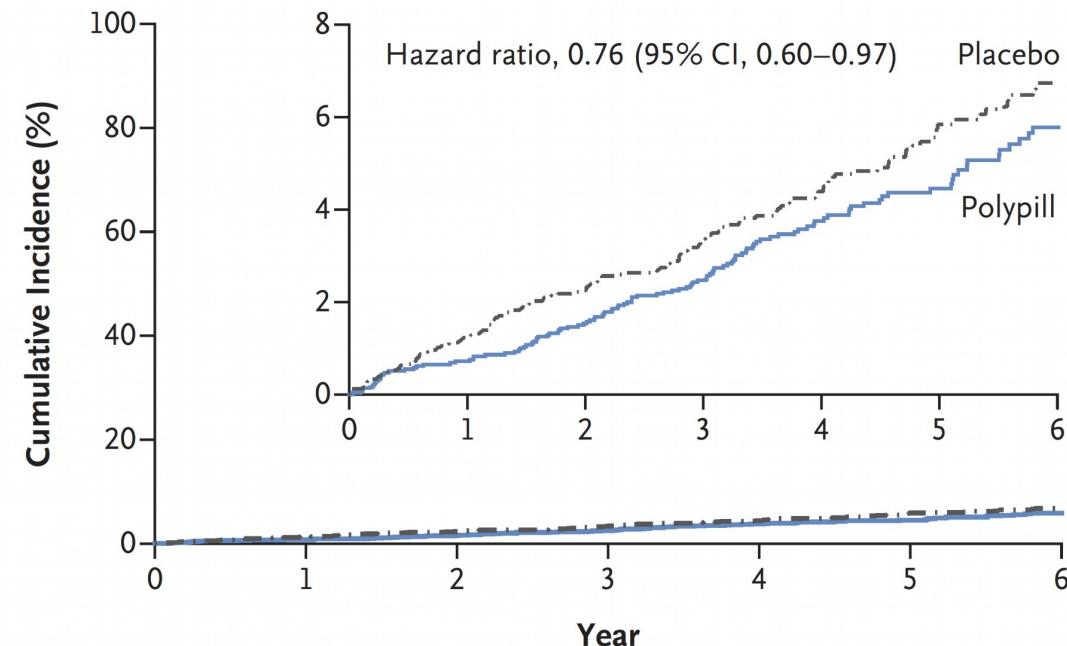
40 mg of simvastatin
100 mg of atenolol
25 mg of hydrochlorothiazide
10 mg of ramipril

**A First Event of the Primary Outcome****No. at Risk**

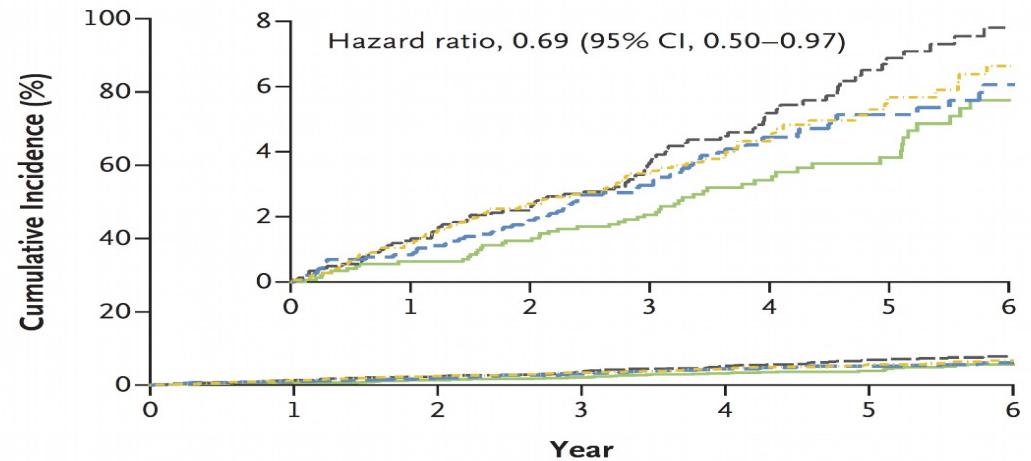
	Placebo	2852	2781	2725	2499	1552	984	634
	Polypill	2861	2814	2759	2536	1581	1020	676

Polypill with or without Aspirin in Persons without Cardiovascular Disease

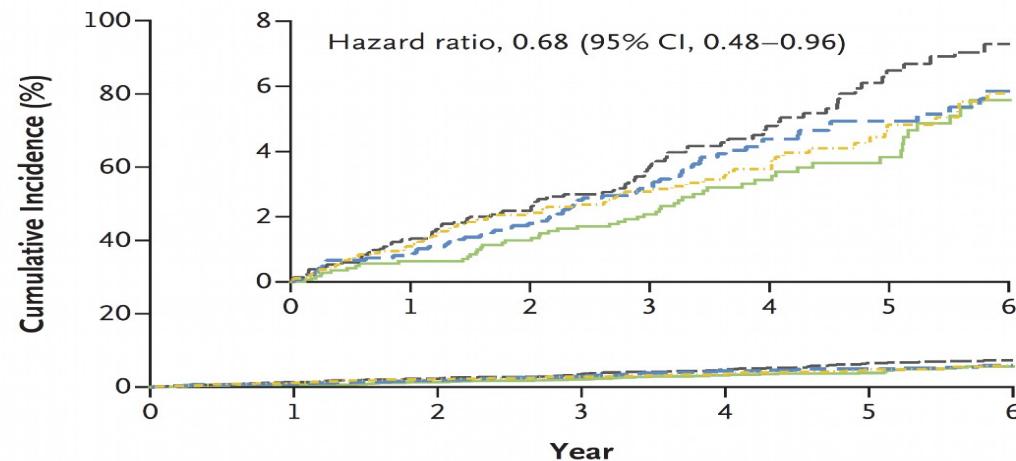
S. Yusuf, P. Joseph, A. Dans, P. Gao, K. Teo, D. Xavier, P. López-Jaramillo, K. Yusoff, A. Santoso, H. Gamra, S. Talukder, C. Christou, P. Girish, K. Yeates, F. Xavier, G. Dagenais, C. Rocha, T. McCready, J. Tyrwhitt, J. Bosch, and P. Pais, for the International Polycap Study 3 Investigators*

B First and Recurrent Events of the Primary Outcome**No. at Risk**

	Placebo	2852	2782	2725	2516	1570	996	716
	Polypill	2861	2818	2760	2610	1620	1055	768

A First Event of the Primary Outcome**No. at Risk**

	1	2	3	4	5	6
Double placebo	1421	1384	1358	1239	767	493
Aspirin only	1431	1397	1367	1260	785	491
Polypill only	1432	1409	1381	1268	790	511
Polypill+aspirin	1429	1405	1378	1268	791	509
						317
						340
						336

B First and Recurrent Events of the Primary Outcome**No. at Risk**

	1	2	3	4	5	6
Double placebo	1421	1387	1363	1246	776	500
Aspirin only	1431	1397	1367	1329	870	501
Polypill only	1432	1412	1382	1326	809	636
Polypill+aspirin	1429	1407	1383	1302	828	528
						356
						364
						390
						387

ORIGINAL ARTICLE

Polypill with or without Aspirin in Persons without Cardiovascular Disease

S. Yusuf, P. Joseph, A. Dans, P. Gao, K. Teo, D. Xavier, P. López-Jaramillo, K. Yusoff, A. Santoso, H. Gamra, S. Talukder, C. Christou, P. Girish, K. Yeates, F. Xavier, G. Dagenais, C. Rocha, T. McCready, J. Tyrwhitt, J. Bosch, and P. Pais, for the International Polycap Study 3 Investigators*

— Double placebo - - - Aspirin only
 - - - Polypill only — Polypill+aspirin

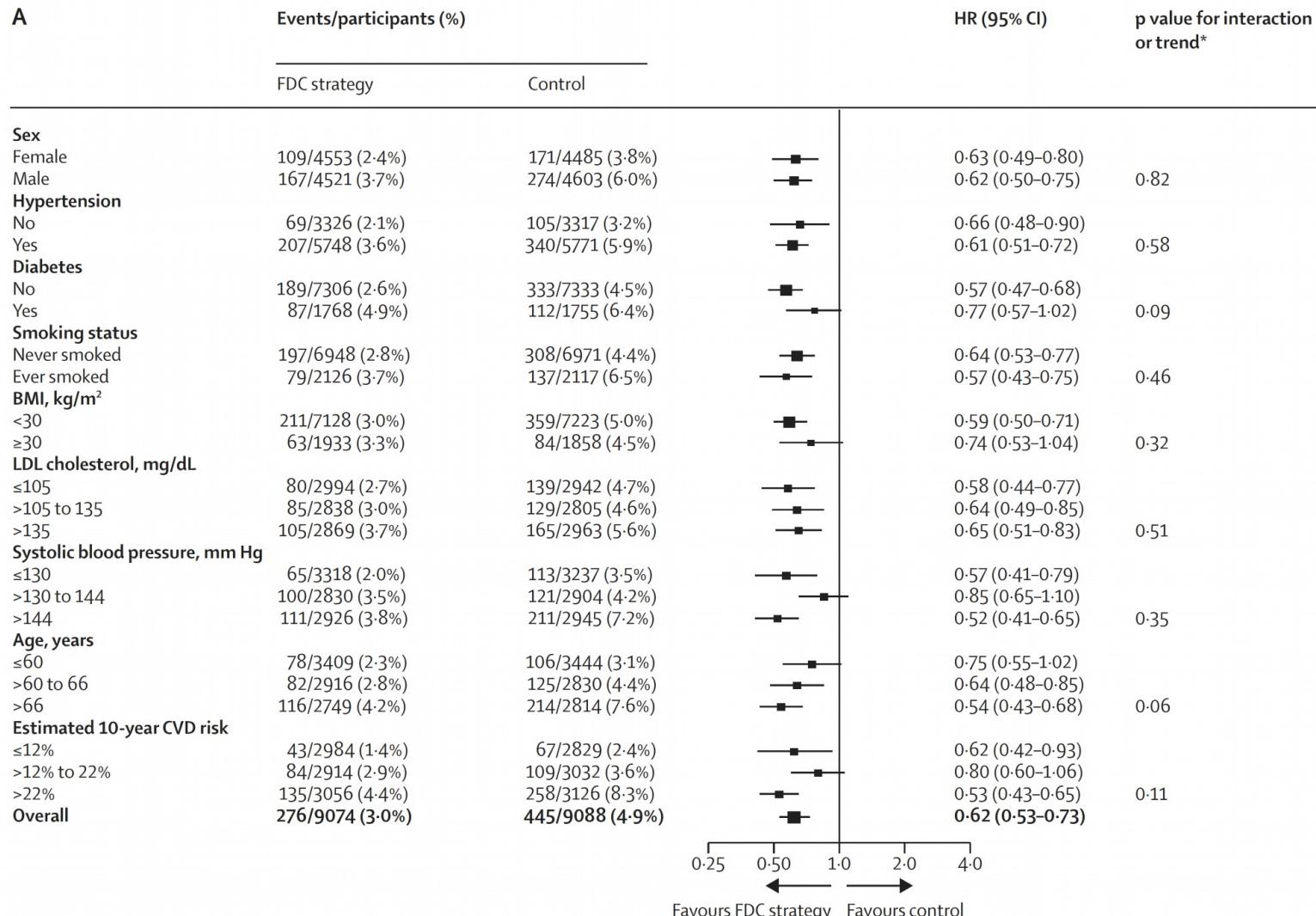
....participants without CVD who had an elevated INTERHEART Risk Score to receive a polypill (containing 40 mg of simvastatin, 100 mg of atenolol, 25 mg of hydrochlorothiazide, and 10 mg of ramipril) or placebo daily, aspirin (75 mg) or placebo daily,



Fixed-dose combination therapies with and without aspirin for primary prevention of cardiovascular disease: an individual participant data meta-analysis

Philip Joseph, Gholamreza Roshandel, Peggy Gao, Prem Pais, Eva Lonn, Denis Xavier, Alvaro Avezum, Jun Zhu, Lisheng Liu, Karen Sliwa, Habib Gamra, Shrikant I Bangdiwala, Koon Teo, Rafael Diaz, Antonio Dans, Patricio Lopez-Jaramillo, Dorairaj Prabhakaran, Jose Maria Castellano, Valentín Fuster, Anthony Rodgers, Mark D Huffman, Jackie Bosch, Gilles R Dagenais, Reza Malekzadeh, Salim Yusuf, on behalf of the Polypill Trialists' Collaboration

A



Effect of FDC strategies versus control on the primary outcome in prespecified subgroups

	Control	Fixed-dose combination strategy	p value
Effects potentially related to statin or blood pressure lowering medication			
Participants included in analysis	9088	9074	..
Muscle pain	787 (8.7%)	634 (7.0%)	<0.0001
Dizziness	834 (9.2%)	1060 (11.7%)	<0.0001
Death due to renal cause	7 (0.1%)	5 (0.1%)	0.77
Reported non-fatal renal failure or death due to renal cause	41 (0.5%)	44 (0.5%)	0.75
Effects potentially related to aspirin			
Participants included in analysis	4489	4462	..
Gastrointestinal bleed	11 (0.2%)	19 (0.4%)	0.15
Haemorrhagic stroke	15 (0.3%)	10 (0.2%)	0.42
Death due to bleeding	4 (0.1%)	2 (<0.1%)	0.69
Peptic ulcer disease	34 (0.8%)	32 (0.7%)	0.90
Dyspepsia	1589 (35.4%)	1489 (33.4%)	0.05
Data are n (%) unless otherwise indicated.			
Table 5: Side-effects and adverse events			

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Polypill Strategy in Secondary Cardiovascular Prevention

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E. Beghi, Y. Bejot, D. Vivas, A. Cordero, B. Ibañez, and V. Fuster, for the SECURE Investigators*

N=2500 Post MI >65



+ At Least One

- a. Documented DM
- b. Mild to moderate CKD
- c. Prior MI
- d. Prior coronary revascularization
- e. Prior stroke
- f. Age \geq 75 years

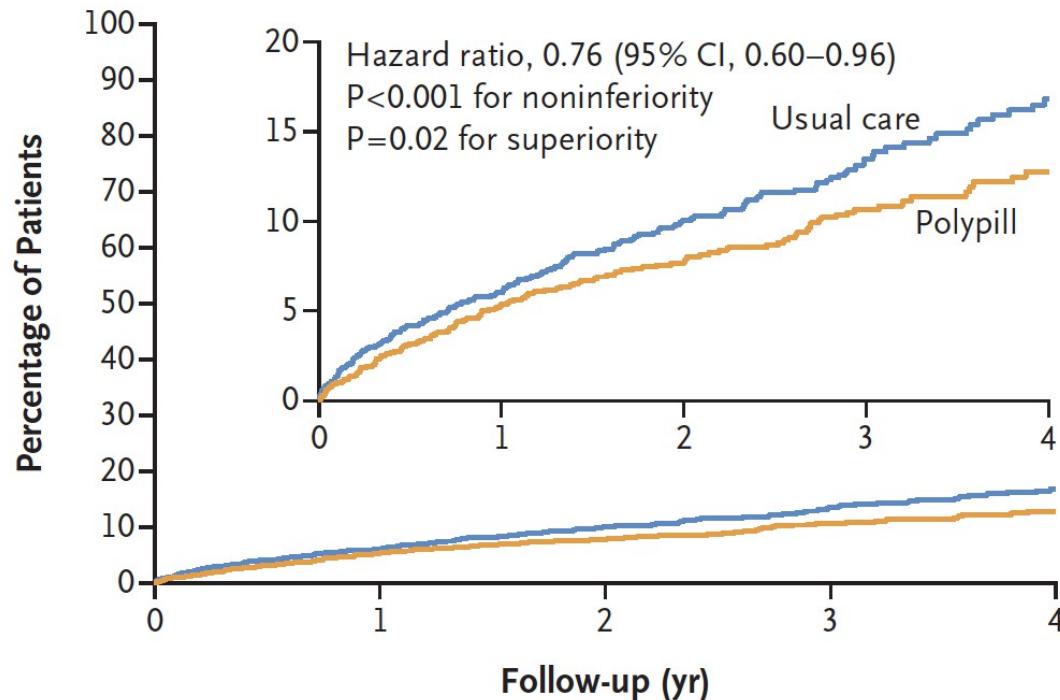
Median FU: 3 years

The primary composite endpoint
cardiovascular death, MI, stroke, or urgent
revascularization.

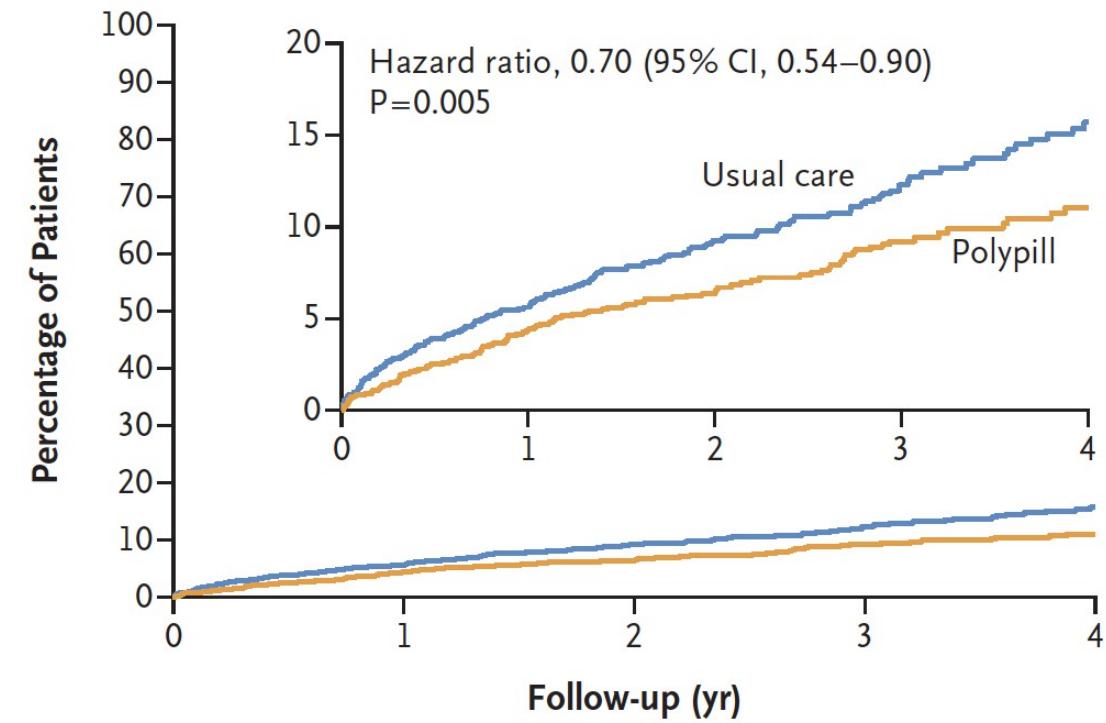
The key secondary endpoint
cardiovascular death, MI, or stroke.

Polypill Strategy in Secondary Cardiovascular Prevention

A Primary Outcome



B Key Secondary Outcome



No. at Risk

	Usual care	Polypill
No. at Risk	1229	1237
Usual care	1075	1064

No. at Risk

	Usual care	Polypill
No. at Risk	1229	1237
Usual care	1079	1074

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Table 2. Treatment Adherence at 6 Months and 24 Months.[‡]

Treatment Adherence	Polypill Group			Usual-Care Group			Risk Ratio (95% CI) [†]		
	No. of Patients	number of patients (percent)			No. of Patients	number of patients (percent)			
		Low	Medium	High		Low	Medium	High	
At 6 mo	1077	59 (5.5)	258 (24.0)	760 (70.6)	1057	100 (9.5)	294 (27.8)	663 (62.7)	1.13 (1.06–1.20)
At 24 mo	881	37 (4.2)	191 (21.7)	653 (74.1)	851	59 (6.9)	254 (29.8)	538 (63.2)	1.17 (1.10–1.25)

* Treatment adherence was measured with the use of the eight-item Morisky Medication Adherence Scale, which ranges from 0 to 8, as follows: low adherence, <6; medium adherence, 6 to <8; and high adherence, 8.

† The risk ratio was calculated as the probability of high treatment adherence as compared with low or medium adherence in the polypill group as compared with the usual-care group. The 95% confidence intervals were not adjusted for multiple testing and should not be used to infer definitive treatment effects.

The polypill in cardiovascular prevention: evidence, limitations and perspective – position paper of the European Society of Hypertension

Antonio Coca^a, Enrico Agabiti-Rosei^{b,c}, Renata Cifkova^d, Athanasios J. Manolis^e,
Josep Redón^f, and Giuseppe Mancia^{g,h}

J Hypertens 2017, 35(8):1546-1553.

Clinical situations in which use of the polypill for secondary prevention of cardiovascular disease may be considered

Patients not adherent to one or more components of drug therapy recommended for secondary cardiovascular prevention

Patients with blood pressure or low-density lipoprotein cholesterol not at the recommended target with free drug administration who have a suspected low adherence to treatment

Patients with adequate control of BP and lipid profile with free antihypertensive and lipid lowering drug administration (substitution strategy)

The use of the polypill and combination therapy to increase adherence to drug therapy may be considered.

IIb

B

2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation



European Heart Journal (2018) 39, 119–177
European Society doi:10.1093/eurheartj/ehx393
of Cardiology



Combination therapy in the management of hypertension and dyslipidemia



² **Synergy**

² **Simplification**

