L'aderenza terapeutica nell'anziano

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Key Issues in Outcomes Research

Medication Adherence
Its Importance in Cardiovascular Outcomes

P. Michael Ho, MD, PhD; Chris L. Bryson, MD, MS; John S. Rumsfeld, MD, PhD

Abstract—Medication adherence usually refers to whether patients take their medications as prescribed (eg, twice daily), as well as whether they continue to take a prescribed medication. Medication nonadherence is a growing concern to clinicians, healthcare systems, and other stakeholders (eg, payers) because of mounting evidence that it is prevalent and associated with adverse outcomes and higher costs of care. To date, measurement of patient medication adherence and use of interventions to improve adherence are rare in routine clinical practice. The goals of the present report are to address (1) different methods of measuring adherence, (2) the prevalence of medication nonadherence, (3) the association between nonadherence and outcomes, (4) the reasons for nonadherence, and finally, (5) interventions to improve medication adherence. (*Circulation.* 2009;119:3028-3035.)

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

C. Everett Koop, MD

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Ritorno al futuro
FIRENZE, 13–16 DICEMBRE 2023
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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

HR (95% C.I.)

Low (<40%) — (8.1%)

Intermediate (40-79%) — (40.5%)

High (>80%) — (51.4%)

0,2 0,3 0,4 0,5 0,6 0,7 0,8 0,9 1 1,1 1,2 1,3 1,4 1,5 1,6

Mazzaglia G, et al. Circulation 2009
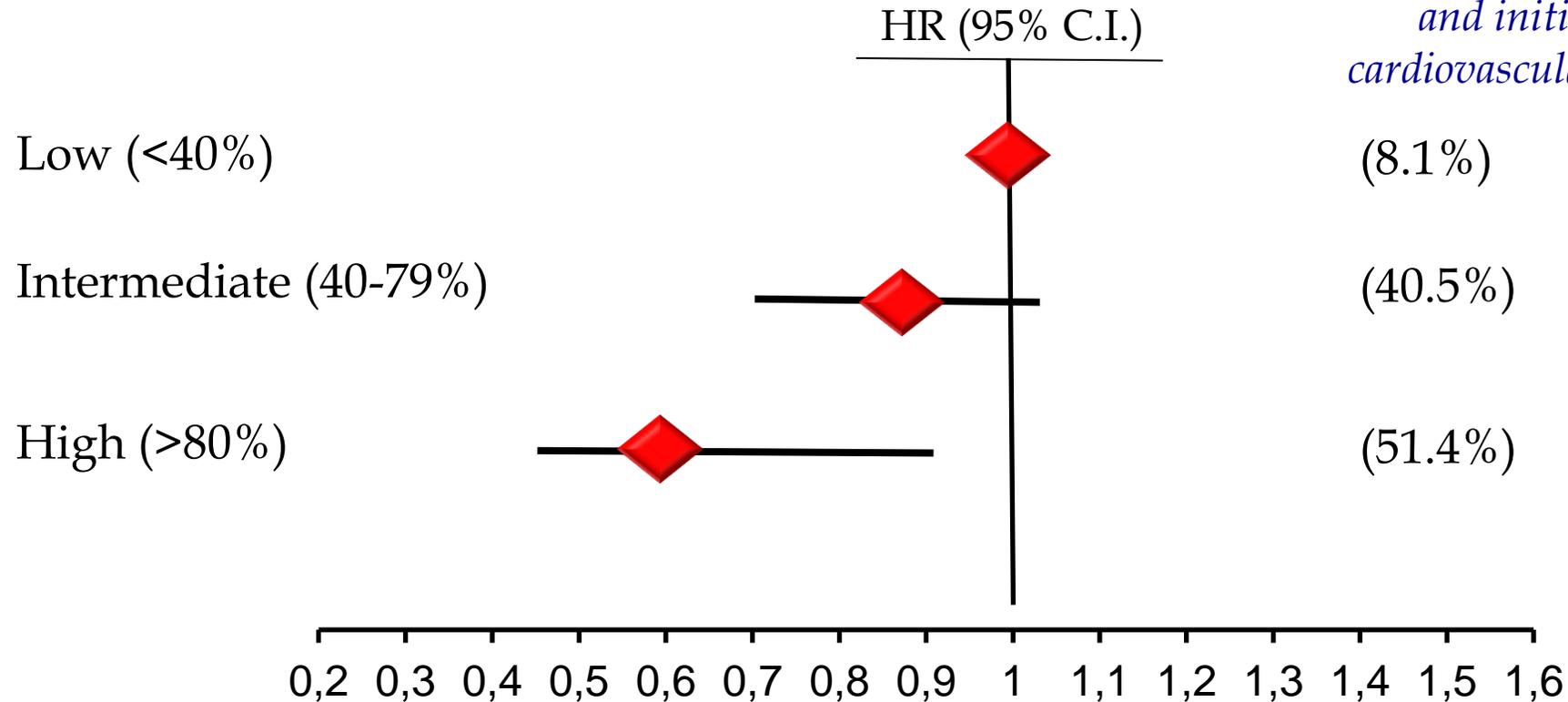
Long term statin adherence inversely associated with all-cause mortality in n Patients With Atherosclerotic Cardiovascular Disease

A retrospective cohort study using data from the **VA Health System** (N=347.104)
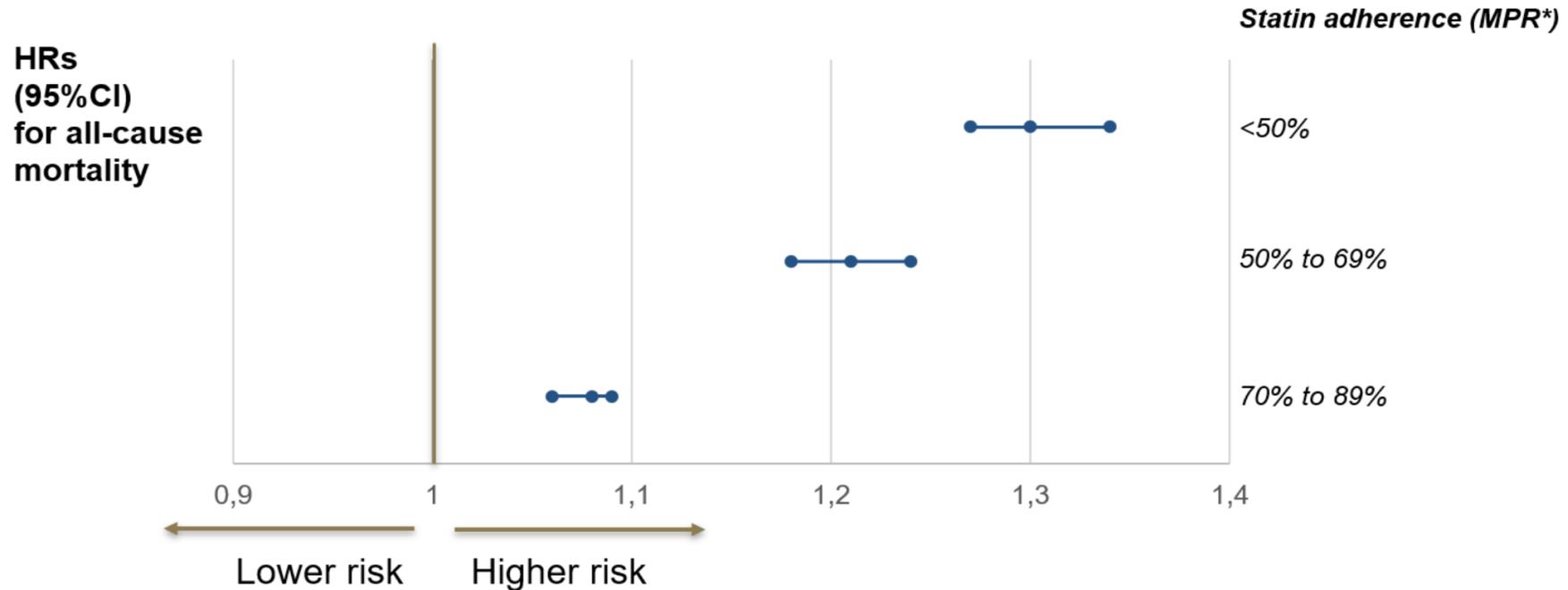

ASCVD: atherosclerotic cardiovascular disease
*MPR (medication possession rate): The number of days of outpatient statin supplied during a 12-month period divided by the number of days that the patient was not hospitalized and alive during the 12-month period

Rodriguez F et al. JAMA Cardiol. 2019 Mar; 4(3): 206–213.

Medication Adherence and Cardiovascular Outcomes:
Rates of MACE-Related Hospitalizations

Bansilal, S. et al. J Am Coll Cardiol. 2016;68(8):789–801.
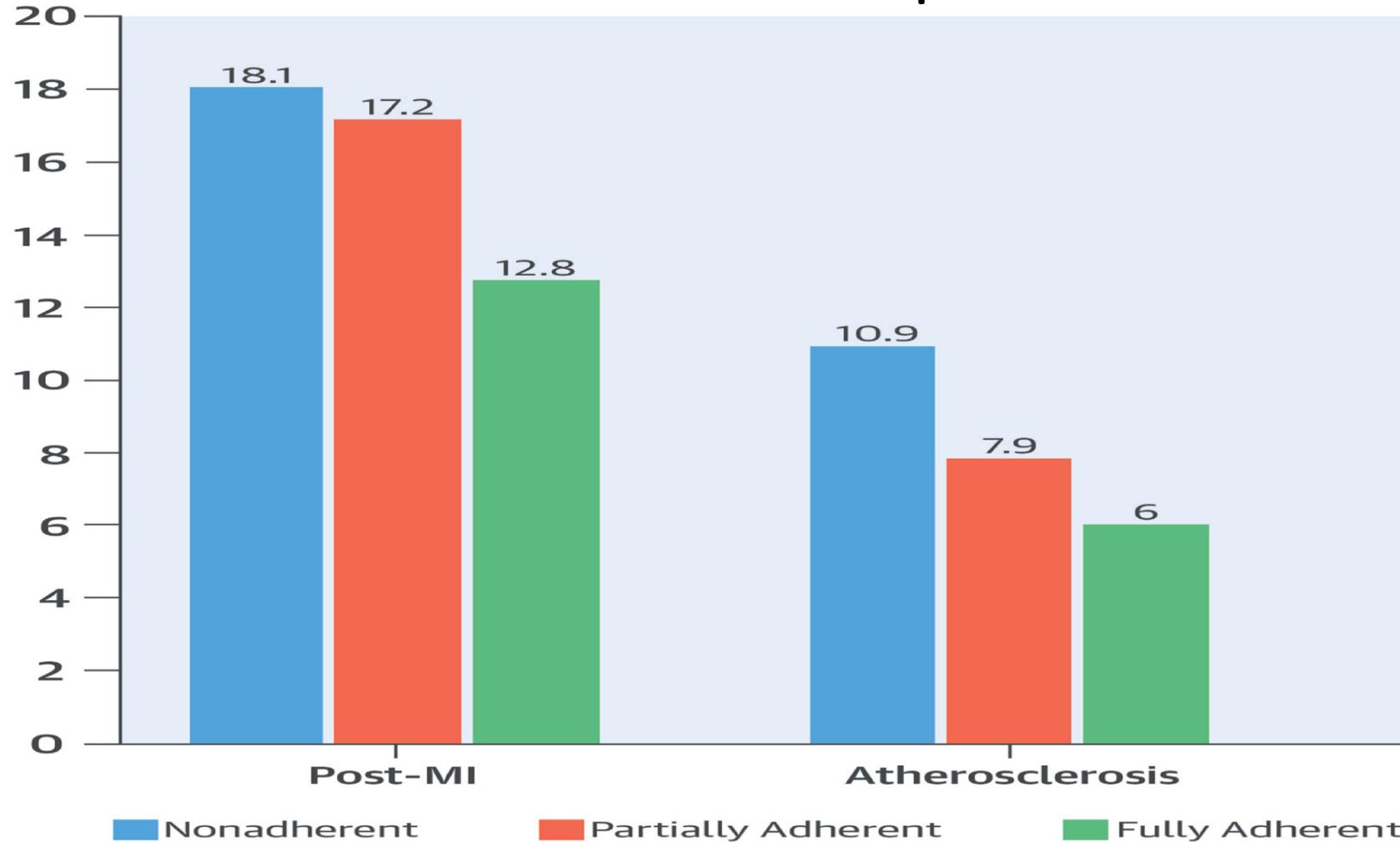
Good adherence is associated with a lower risk of events

Compared with patients with low (<80%) adherence, those with high (≥80%) adherence showed:

Chronic heart failure	Coronary artery disease	Cerebrovascular disease
−11% (CI 0.80–0.99)[1]	−10% (CI 0.84–0.95)[2]	−22% (CI 0.70–0.87)[3]

Relative risk reduction (%)
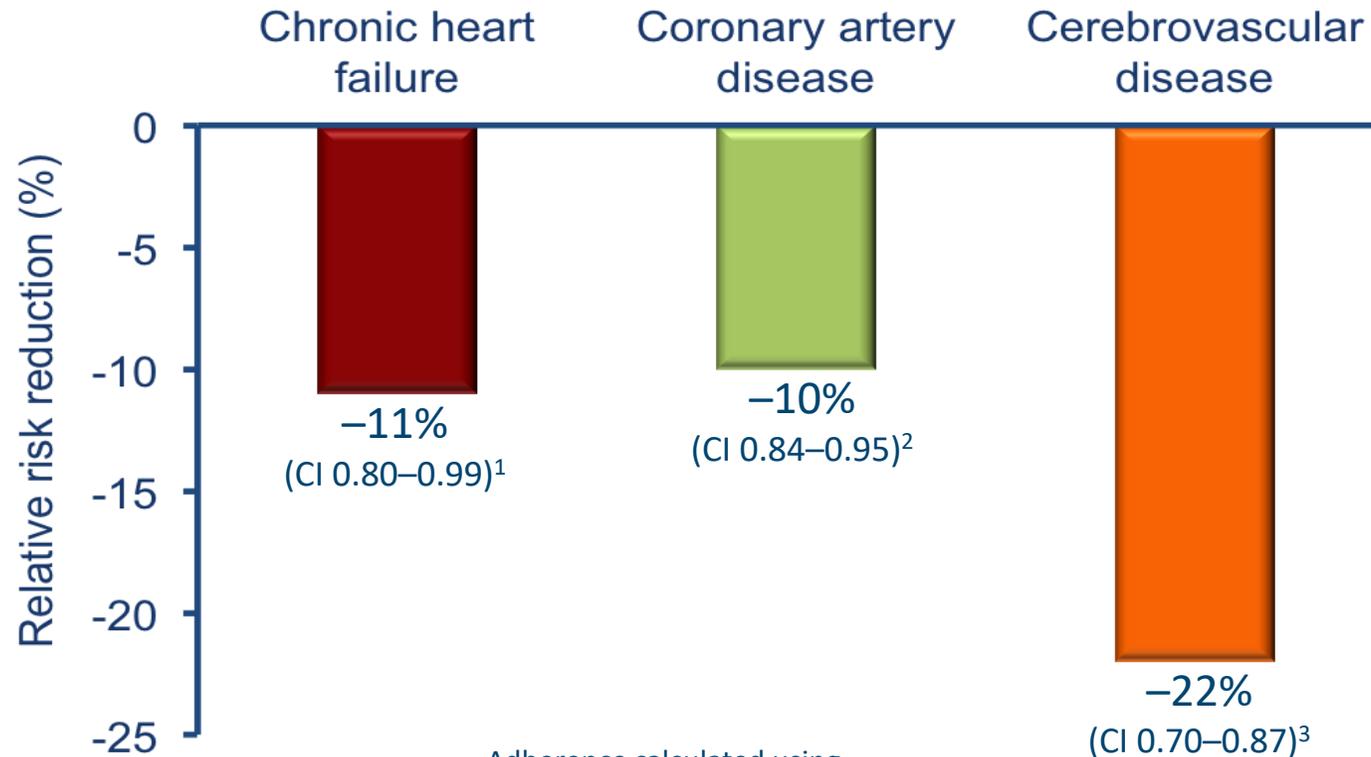
Adherence calculated using medication possession ratio: total number of days' supply of dispensed medication divided by duration of follow up

1. Perreault, Dragomir, White, et al. J Intern Med 2009;266:207–18
2. Perreault, Dragomir, Roy, et al. Br J Clin Pharmacol 2010;69:74–84
3. Kettani, Deragomir, Côté, et al. Stroke 2009;40:213–20

Mutazioni genetiche/ Storia familiare
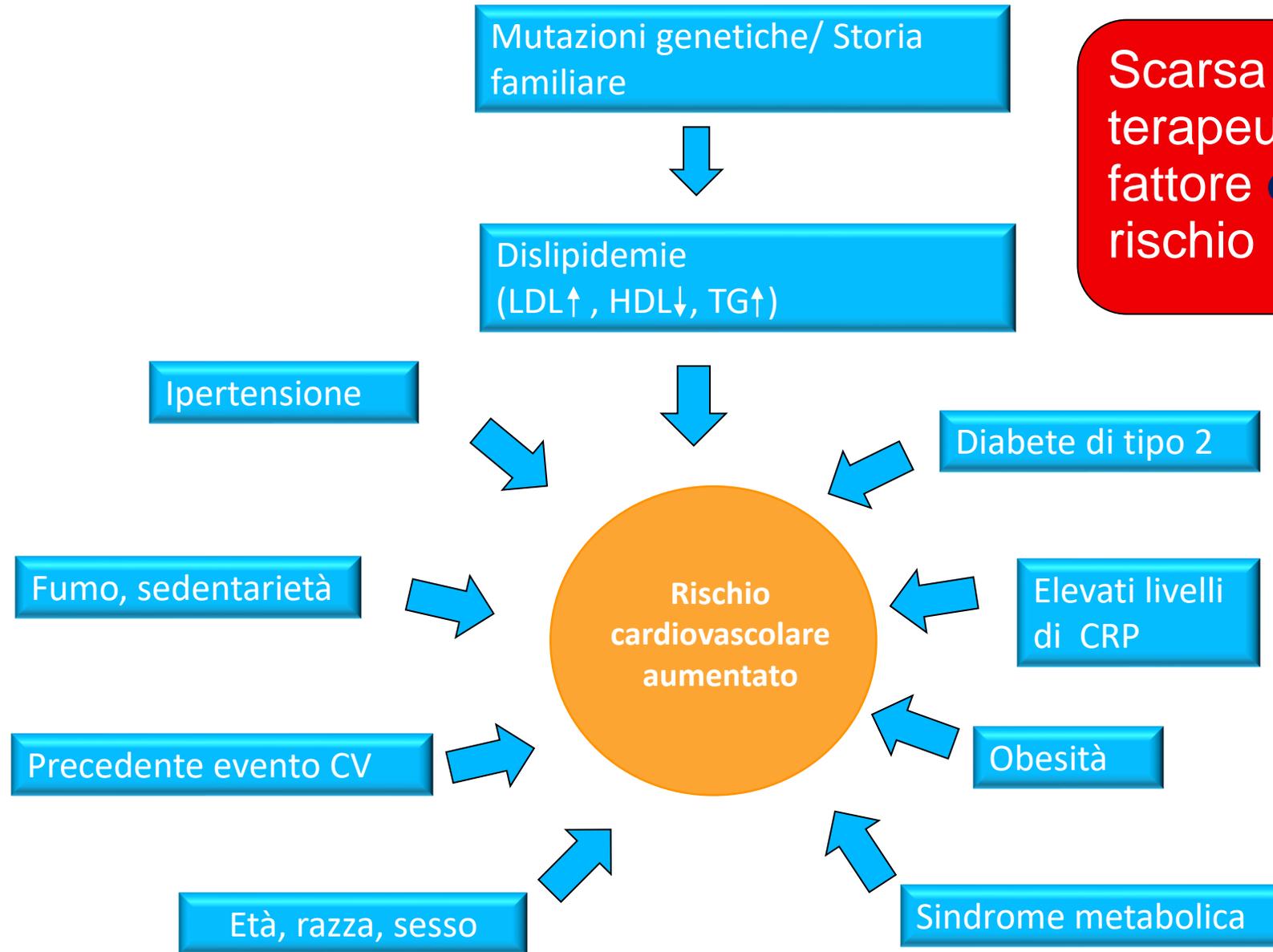
Scarsa aderenza terapeutica: un fattore **occulto** di rischio

Dislipidemie
(LDL↑ , HDL↓, TG↑)

Ipertensione

Diabete di tipo 2

Fumo, sedentarietà

Rischio cardiovascolare aumentato

Elevati livelli di CRP

Precedente evento CV

Obesità

Età, razza, sesso

Sindrome metabolica

LaRosa JC. Curr Atheroscler Rep 2000;2:1-4

2023 ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension

Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA)

Screening for **non-adherence** to treatment is recommended in all patients with apparent resistant hypertension.	I	A
Consider screening for **non-adherence** patients who are on combination treatment (i.e. at least 2 drugs) and have an inadequate BP response to this treatment.	II	C
Check adherence prior to screening for secondary hypertension.	I	A

Indicatori di aderenza al trattamento con farmaci **l'ipertensione e lo scompenso cardiaco** nella popolazione di età ≥45 anni nel periodo 2019-2022 e variazione 2022-2021

	Alta aderenza*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Totale N=273.179						**Nord N=127.331**					
45-54 anni	54,8	54,9	54,0	54,0	-1	-1	56,7	56,8	55,6	55,1	-3	-1
55-64 anni	55,4	54,6	54,7	54,1	-2	-2	56,5	56,0	55,9	55,2	-2	-1
65-74 anni	53,9	53,0	53,9	53,0	-2	-2	54,6	54,3	54,5	54,0	-1	-1
75-84 anni	49,5	48,2	49,7	49,1	-1	-1	50,6	49,5	51,1	50,4	0	-1
≥85 anni	41,0	40,9	42,7	40,9	0	0	42,1	43,0	44,6	43,8	4	-2
Femmine	48,7	48,1	48,6	47,9	-2	-2	49,9	49,5	49,9	49,4	-1	-1
Maschi	58,0	57,3	57,8	57,3	-1	-1	58,7	58,5	58,6	58,0	-1	-1
Totale	**53,1**	**52,5**	**53,0**	**52,4**	**-1**	**-1**	**54,1**	**53,8**	**54,0**	**53,5**	**-1**	**-1**
	Centro N=56.128						**Sud N=89.720**					
45-54 anni	55,8	55,9	55,5	56,1	1	1	52,3	52,2	51,3	51,4	-2	-2
55-64 anni	56,7	55,7	56,4	55,8	-2	-2	53,5	52,2	52,1	51,6	-3	-3
65-74 anni	55,9	53,5	54,9	55,0	-2	-2	51,8	51,1	52,2	50,1	-3	-3
75-84 anni	50,0	48,7	50,2	50,0	0	0	47,3	45,6	46,5	46,1	-2	-2
≥85 anni	41,2	39,5	42,5	40,2	-2	-2	39,0	38,8	39,6	36,2	-7	-7
Femmine	49,5	48,4	49,4	49,4	0	0	46,7	46,1	46,3	45,0	-4	-4
Maschi	59,5	58,2	59,4	59,1	-1	-1	56,2	55,2	55,6	55,2	-2	-2
Totale	**54,1**	**53,0**	**54,1**	**53,9**	**0**	**0**	**51,2**	**50,5**	**50,8**	**49,9**	**-3**	**-3**

L'uso dei Farmaci in Italia
Rapporto Nazionale
Anno 2022

OSSERVATORIO NAZIONALE SULL'IMPIEGO DEI MEDICINALI

Indicatori di aderenza al trattamento con farmaci **ipolipemizzanti** nella popolazione di età ≥45 anni nel periodo 2019-2022 e variazione 2022-2021

L'uso dei Farmaci in Italia
Rapporto Nazionale
Anno 2022

OSSERVATORIO NAZIONALE SULL'IMPIEGO DEI MEDICINALI

	Alta aderenza*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Totale N=290.263						**Nord N=127.468**					
45-54 anni	40,2	41,7	42,7	42,3	-1	5	43,1	45,9	46,2	45,3	-2	5
55-64 anni	41,5	42,2	43,8	43,7	0	5	44,6	45,1	46,8	46,5	-1	4
65-74 anni	40,3	41,8	42,6	43,4	2	8	42,7	44,7	45,3	45,8	1	7
75-84 anni	40,6	41,9	42,2	43,7	4	8	43,1	43,9	44,5	46,1	4	7
≥85 anni	40,7	41,6	40,9	42,0	3	3	43,0	44,4	43,5	44,6	2	4
Femmine	35,7	37,2	38,1	39,1	3	10	38,2	39,5	40,5	41,6	3	9
Maschi	46,3	47,2	48,4	48,3	0	4	48,8	50,2	51,2	50,9	-1	4
Totale	**40,7**	**41,9**	**42,8**	**43,3**	**1**	**6**	**43,4**	**44,8**	**45,6**	**46,0**	**1**	**6**
	Centro N=58.627						**Sud N=104.168**					
45-54 anni	41,7	40,8	42,8	43,0	0	3	37,2	38,6	39,3	38,9	-1	5
55-64 anni	42,1	42,8	44,2	44,0	0	5	38,2	39,4	40,5	40,3	-1	5
65-74 anni	40,9	41,8	42,2	44,1	5	8	37,5	38,8	39,5	40,0	1	7
75-84 anni	40,9	42,0	41,5	42,9	3	5	37,2	39,2	39,1	40,4	3	9
≥85 anni	42,5	42,2	41,4	43,8	6	3	36,8	38,1	37,0	37,2	1	1
Femmine	36,4	37,0	38,1	39,5	4	8	32,9	35,0	35,3	35,9	2	9
Maschi	47,1	47,7	48,2	48,6	1	3	43,1	43,8	45,0	44,7	-1	4
Totale	**41,4**	**42,0**	**42,7**	**43,6**	**2**	**5**	**37,6**	**39,0**	**39,7**	**39,9**	**1**	**6**

https://www.aifa.gov.it/-/l-uso-dei-farmaci-in-italia-rapporto-osmed-2022

Indicatori di aderenza al trattamento con farmaci **anticoagulanti** nella popolazione di età ≥45 anni nel periodo 2019-2022 e variazione 2022-2021

	Alta aderenza*											
	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19	2019	2020	2021	2022	Δ % 22-21	Δ % 22-19
	Totale N=70.561						Nord N=35.059					
45-54 anni	62,8	62,7	64,0	62,1	-3	-1	66,5	63,5	65,5	64,3	-2	-3
55-64 anni	64,9	66,1	69,8	64,5	-8	-1	65,3	66,1	70,1	67,3	-4	3
65-74 anni	64,0	67,2	68,8	64,8	-6	1	63,5	68,3	70,5	67,3	-5	6
75-84 anni	47,0	50,1	49,5	47,5	-4	1	47,1	51,9	51,8	49,9	-4	6
≥85 anni	25,5	25,9	24,2	24,5	1	-4	26,2	27,9	25,3	25,7	2	-2
Femmine	46,0	47,9	49,4	47,6	-4	4	45,3	48,4	49,8	48,7	-2	8
Maschi	53,1	55,8	58,8	55,1	-6	4	53,4	57,5	60,8	57,8	-5	8
Totale	**49,6**	**52,0**	**54,3**	**51,6**	**-5**	**4**	**49,6**	**53,2**	**55,7**	**53,6**	**-4**	**8**
	Centro N=14.324						Sud N=14.324					
45-54 anni	56,1	60,8	59,3	60,3	2	8	62,1	62,6	65,0	59,7	-8	-4
55-64 anni	61,0	64,2	68,8	62,7	-9	3	66,5	67,2	69,9	61,5	-12	-8
65-74 anni	60,0	65,4	67,0	61,7	-8	3	66,9	66,9	67,7	62,8	-7	-6
75-84 anni	45,3	48,8	48,8	46,4	-5	2	47,8	48,1	46,3	43,7	-6	-9
≥85 anni	22,9	25,4	24,3	23,7	-2	3	26,3	23,3	22,2	22,8	3	-13
Femmine	42,3	46,1	47,0	44,7	-5	6	48,9	48,6	50,7	47,9	-6	-2
Maschi	49,6	53,4	56,6	53,1	-6	7	54,8	55,0	57,3	51,8	-10	-5
Totale	**46,0**	**49,8**	**52,0**	**49,1**	**-6**	**7**	**51,8**	**51,8**	**54,0**	**49,9**	**-8**	**-4**

https://www.aifa.gov.it/-/l-uso-dei-farmaci-in-italia-rapporto-osmed-2022

L'uso dei Farmaci in Italia
Rapporto Nazionale Anno 2022

OSSERVATORIO NAZIONALE SULL'IMPIEGO DEI MEDICINALI

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Determinanti del successo (o dell'insuccesso...) terapeutico

➤ Inerzia terapeutica da parte del medico nel perseguire il raggiungimento dei target terapeutici

Global report on hypertension: the race against a silent killer
19 September 2023
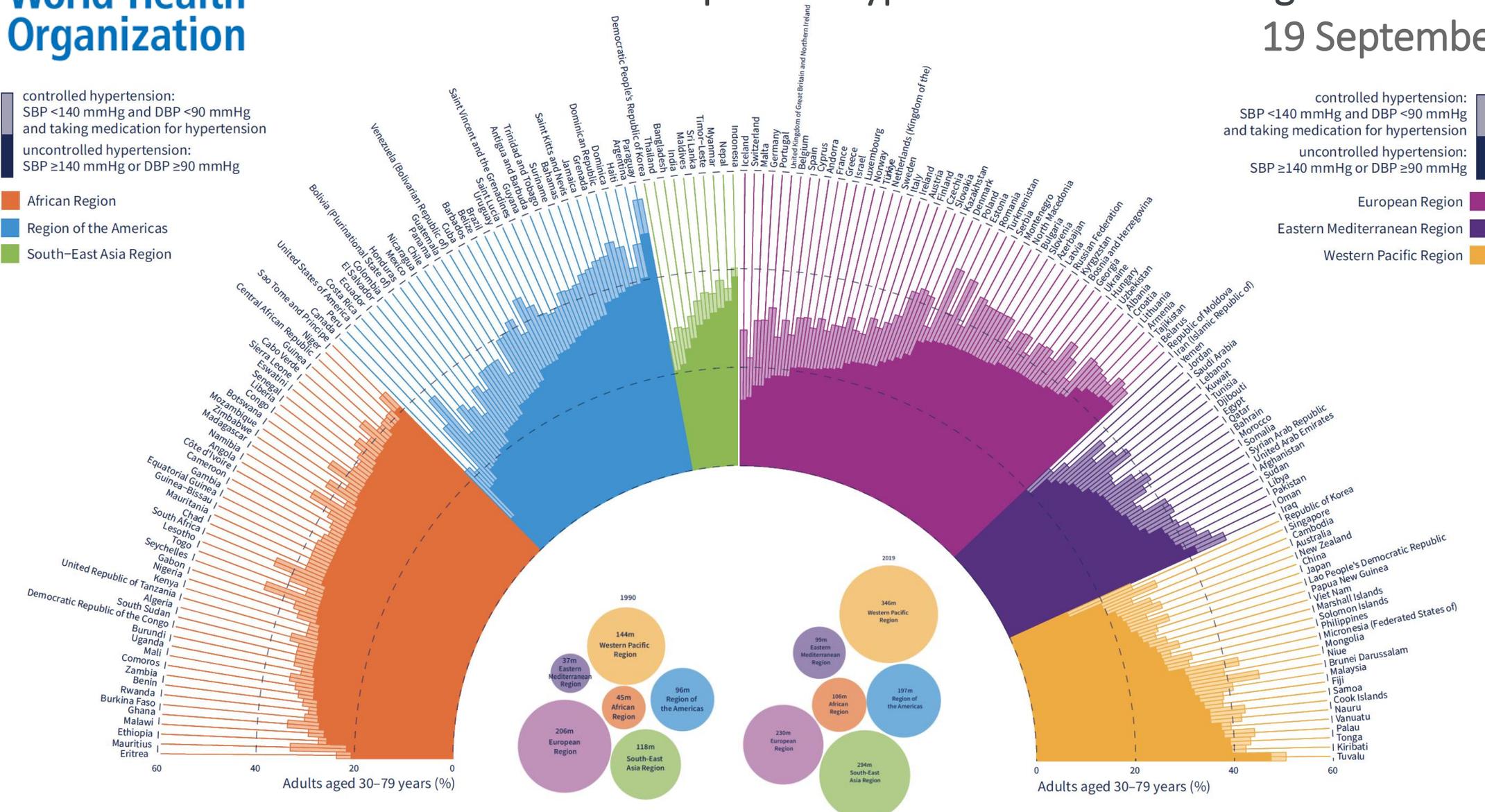
Office BP targets in the general adult hypertensive population

Systolic BP target / **Diastolic BP target**

Most patients[a]

Target — Avoid
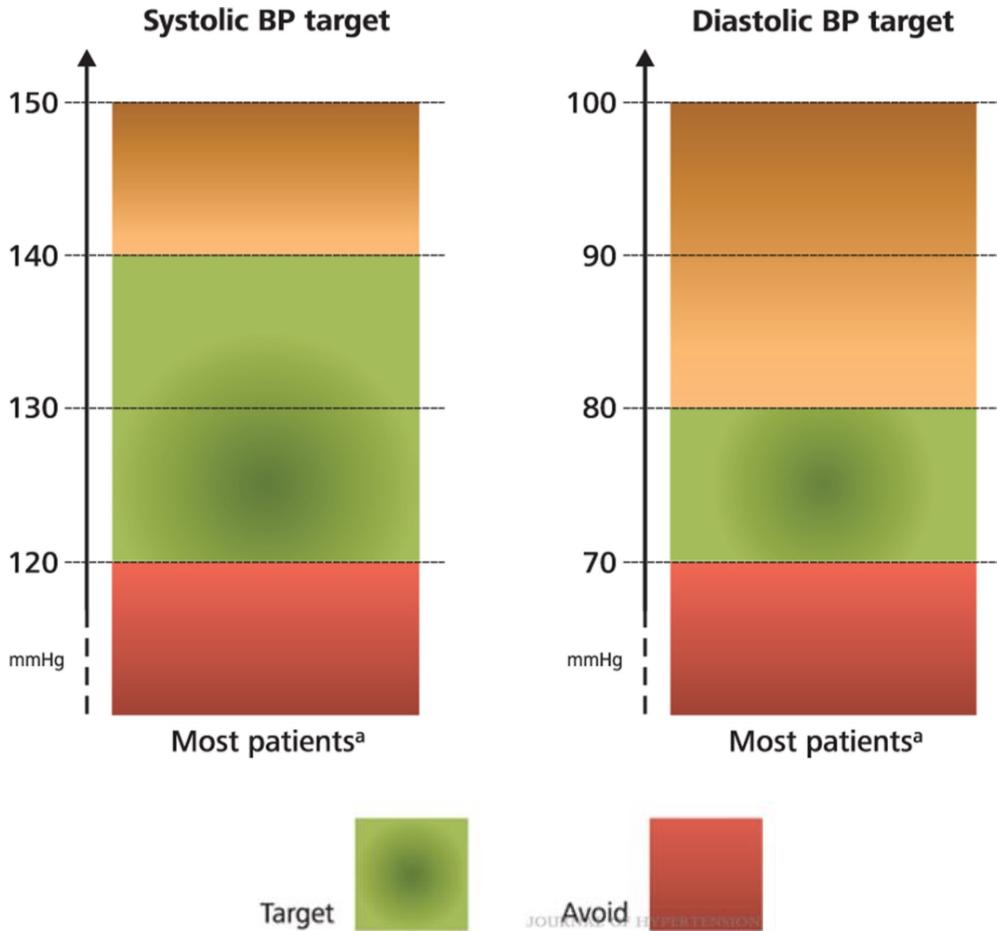
TABLE 21. Adapting BP-lowering strategies in patients older than 80 years according to their functional/autonomy status

Characteristics	Group 1 Fit	Group 2 Slowed but autonomous for most activities	Group 3 Severely dependent
Diagnosis	-ADL (Katz) ≥5/6 and -absence of clinically significant dementia (MMSE≤20/30) and -routine walking activities	-Profile between Groups 1 and 3	-ADL (Katz) ≤2/6 or -severe dementia or -(MMSE ≤10/30), chronic bedridden or -end of life
Therapeutic strategy	- As recommended below	-Individualize treatment	-Individualize treatment -Prioritize therapeutic strategies according to comorbidities and polypharmacy issues

Katz Index of Independence in Activities of Daily Living (ADL) is a scale rated from 0 (completely dependent) to 6 (completely autonomous). This scale comprises 6 ADL: Bathing, Dressing, Toileting, Transferring, Feeding and Continence. For each ADL, '0' means that the person is unable to do it without assistance, 0.5 need of some assistance, 1 no need of any assistance [973]. MMSE, Mini mental status evaluation.

Prioritize therapeutic strategies according to comorbidities and polypharmacy issues

Treatment With Multiple Blood Pressure Medications, Achieved Blood Pressure, and Mortality in Older (≥80 ys)Nursing Home Residents - The PARTAGE Study

A

Unadjusted analysis	HR (95% CI)		P Value
SBP <130 mm Hg	0.83 (0.53-1.31)		.42
≥2 Anti-HTN drugs	0.97 (0.70-1.33)		.83
SBP <130 mm Hg and ≥2 anti-HTN drugs	2.13 (1.23-3.69)		.007
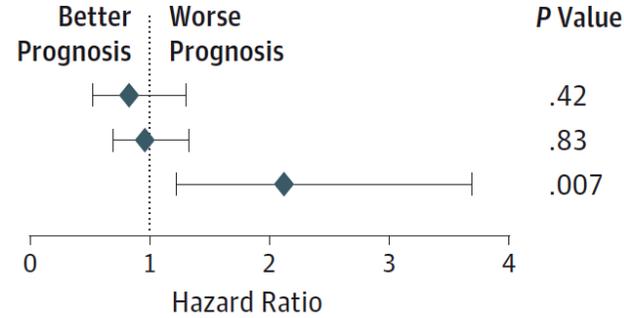
B

Adjusted analysis	HR (95% CI)		P Value
SBP <130 mm Hg	0.75 (0.46-1.22)		.25
≥2 Anti-HTN drugs	1.16 (0.82-1.64)		.41
SBP <130 mm Hg and ≥2 anti-HTN drugs	2.09 (1.16-3.77)		.01
Age, per 5 y	1.25 (1.10-1.42)		<.001
Male sex	1.63 (1.22-2.17)		<.001
BMI ≤25	1.57 (1.19-2.06)		.001
Charlson Comorbidity Index score, per 1-point increase	1.09 (1.03-1.16)		.005
ADL score, per 1-point increase	0.77 (0.68-0.86)		<.001
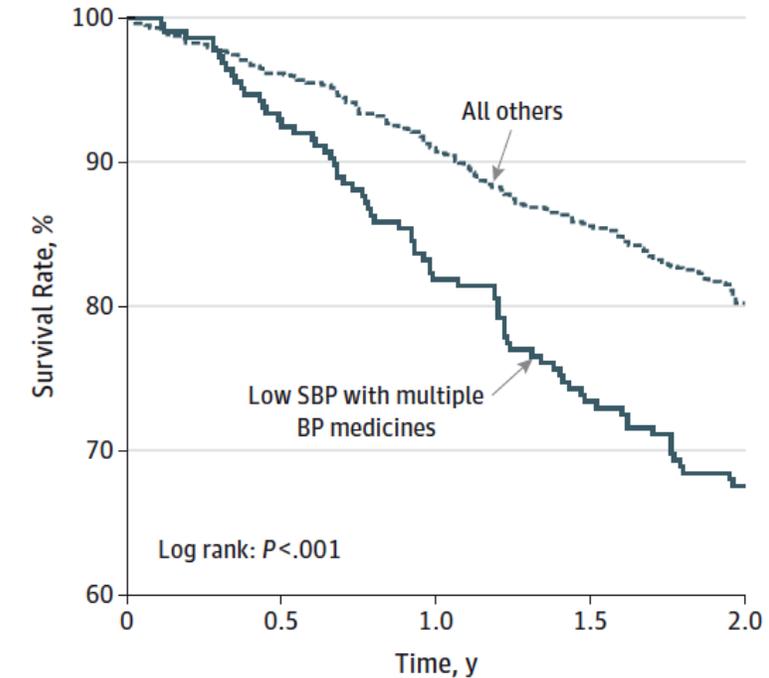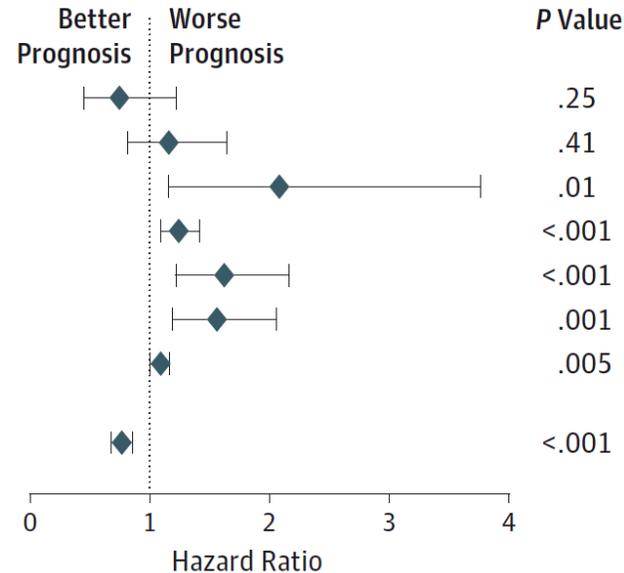
Patients Left at Risk

Low SBP with multiple BP medicines	227	210	184	163	70
All others	900	859	800	747	271
SBP/anti-HTN drugs					
<130 mm Hg/<2	149	145	138	126	49
≥130 mm Hg/≥2	423	404	376	360	129
≥130 mm Hg/<2	328	310	286	261	93

Benetos A et al. JAMA Intern Med. 2015;175(6):989-995.

Generalizability of Blood Pressure Lowering Trials to OlderPatients: Cross-Sectional Analysis

Total

With CV disease

Less fit or frail

Eligible for
- HYVET & SPRINT: 1.0%
- SPRINT & OPTiMISE: 10.2%

Eligible for
- HYVET & SPRINT: 0.3%
- SPRINT & OPTiMISE: 7.6%

Eligible for
- HYVET & SPRINT: 0.6%
- SPRINT & OPTiMISE: 9.4%
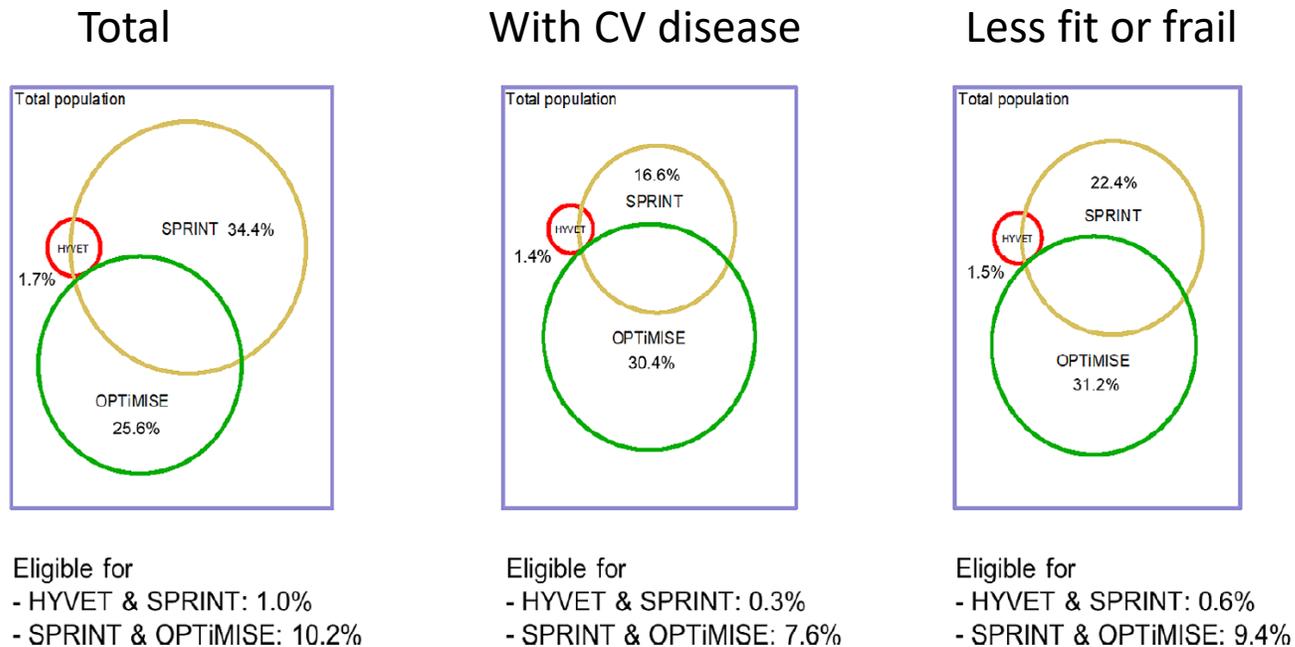
➢ 24 general practices in England.
➢ 15,376 patients identified, aged 80 and older

Sheppard JP et al. J Am Geriatr Soc 68:2508-2515, 2020.

HYVET
- SBP normal or controlled: 64.5%
- SBP too high or uncontrolled: 30.7%
- Dementia: 12.6%
- Heart failure: 8.0%
- DBP too high or uncontrolled: 5.5%
- DBP normal or controlled: 4.3%
- SCr too high: 2.5%
- Terminal illness: 0.2%
- Secondary hypertension: 0.1%

SPRINT
- SBP normal or controlled: 38.2%
- Diabetes: 16.5%
- Stroke or TIA: 14.6%
- Dementia: 12.6%
- SBP too high or uncontrolled: 5.6%
- Orthostatic hypotension: 5.1%
- Proteinuria: 2.9%
- Terminal illness: 0.2%
- Secondary hypertension: 0.1%

OPTIMISE
- SBP normal or controlled: 43.0%
- SBP too high or uncontrolled: 27.2%
- Dementia: 12.6%
- Left ventricular dysfunction: 2.4%
- Terminal illness: 0.2%
- Secondary hypertension: 0.1%

BP Control in Older Adults: Toward a More Personalized Medicine Approach

*But these metrics come with **confounding biases** and leave many older adults vulnerable to new disability, over- or undertreatment, and otherwise poor care from inadequate evidence.*

*Together, **observational studies and randomized controlled trials can provide the evidence to inform individualized care across the spectrum of older people**.*

*This is the best common ground on which to stand scientifically and clinically. **Patients expect no less of us**.*

Let us hope that the young scientists watching us will observe us finding common ground and continue to follow this principle in the conduct of future research.
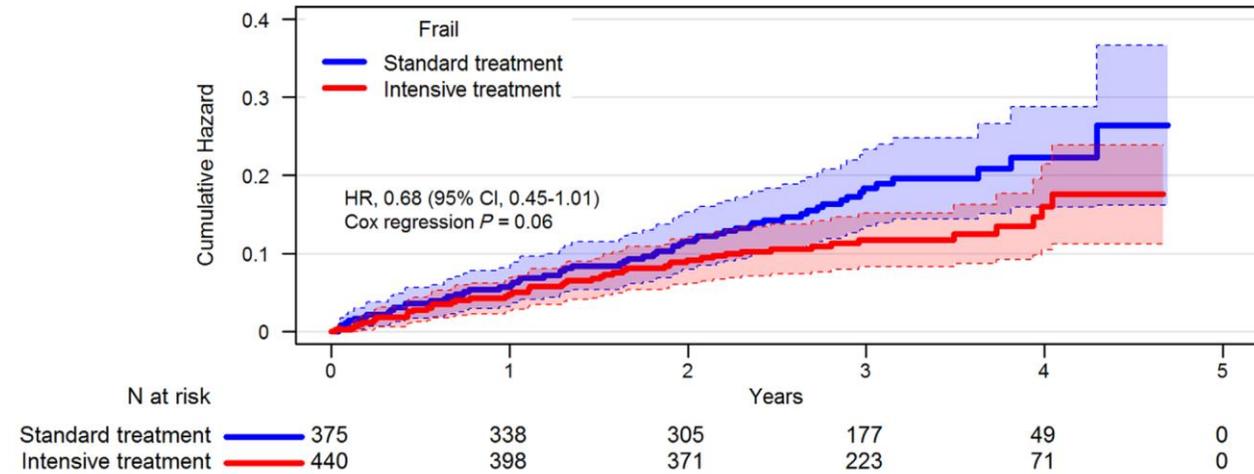
...Many geriatricians went into academic geriatrics because we were caring for larger and larger numbers of older people during training without guidelines for individualizing patient care of this group.
The only guide was "experience" or "extrapolation."

Williamson JD et al. JAGS 68:2489-2491, 2020

EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DAVINCI study

The primary prevention group summarized by level of risk and statin regimen.
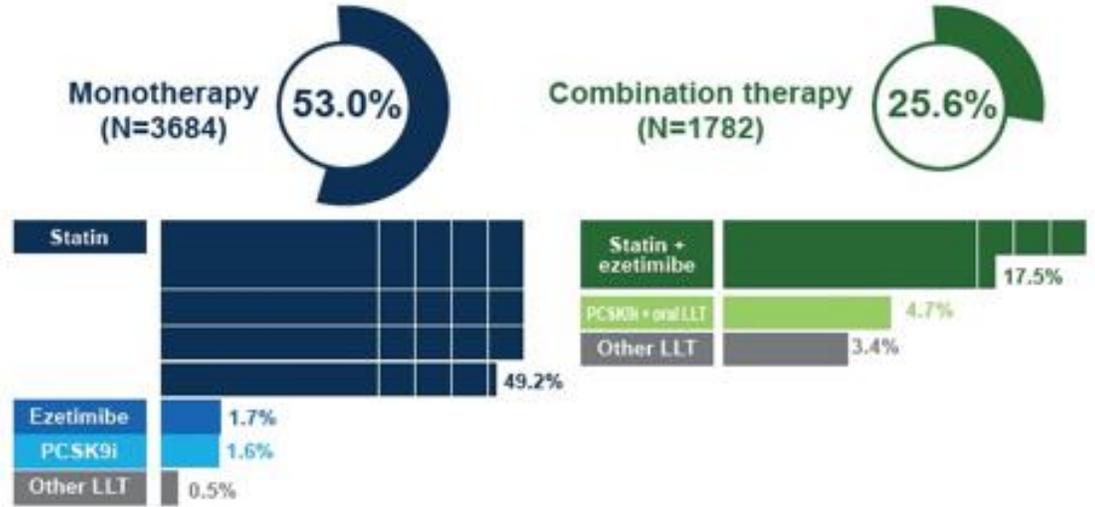
Ray KK et al. Eur J Prev Cardiol 2021

Catapano et al., presented at ESC congress 2022
Arca et al, presented at SIC congress 2022

ESC European Society of Cardiology

ESC/EAS GUIDELINES

Legend:
- Older (blue)
- Elderly (red)
- Very Elderly (green)
- Oldest Old (purple)
- Octagenarian (orange)
- Nonagenarian (black)
- Frail (brown)

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)
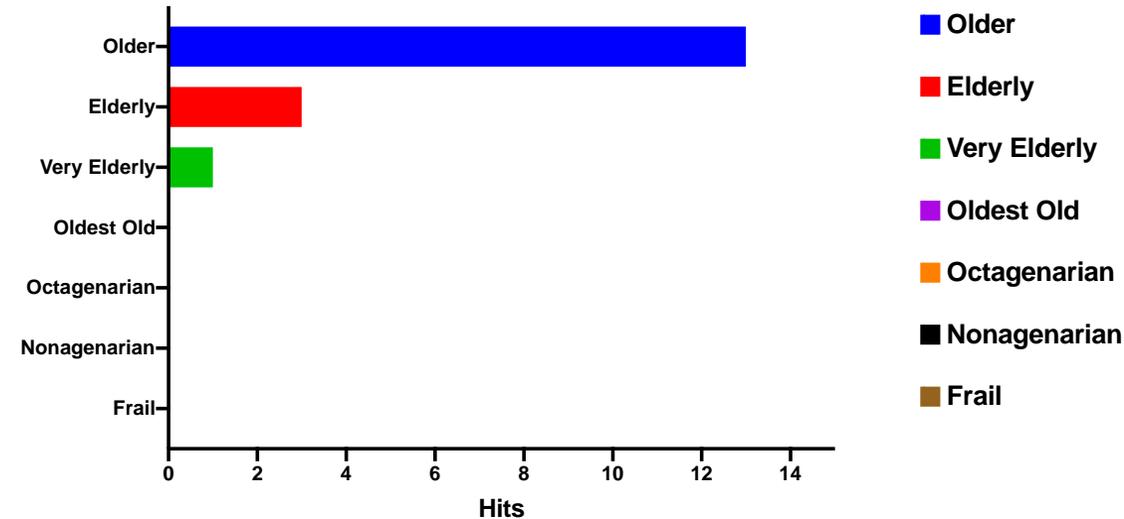
Recommendations for the treatment of dyslipidaemias in older people (aged >65 years)

Recommendations	Class[a]	Level[b]
Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.[217]	I	A
Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged ≤75 years.[217]	I	A

ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.
[a]Class of recommendation.
[b]Level of evidence.

Mach F et al. European Heart Journal (2020) 41, 111188

Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials

Cholesterol Treatment Trialists' Collaboration*

CTT, Lancet 2019; 393: 407–15
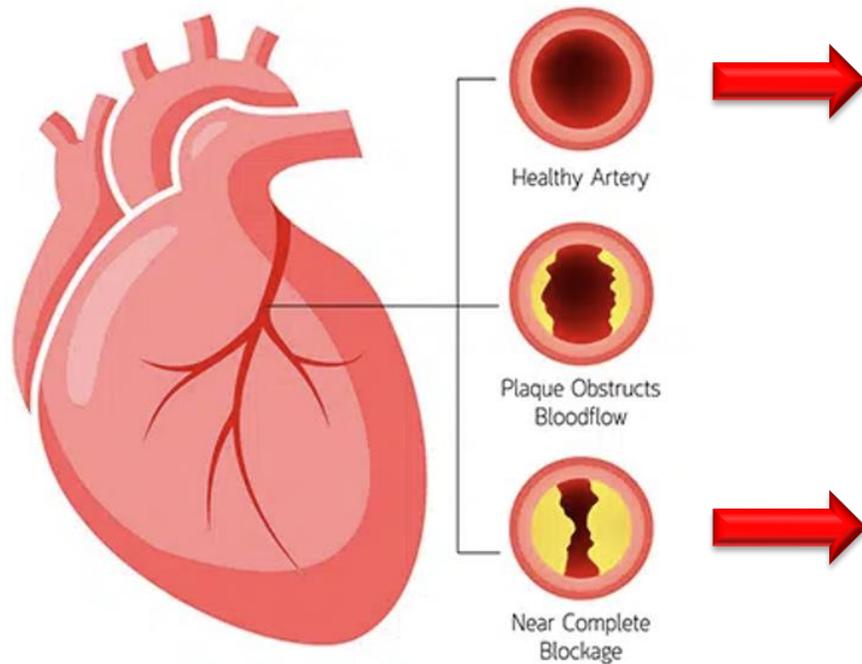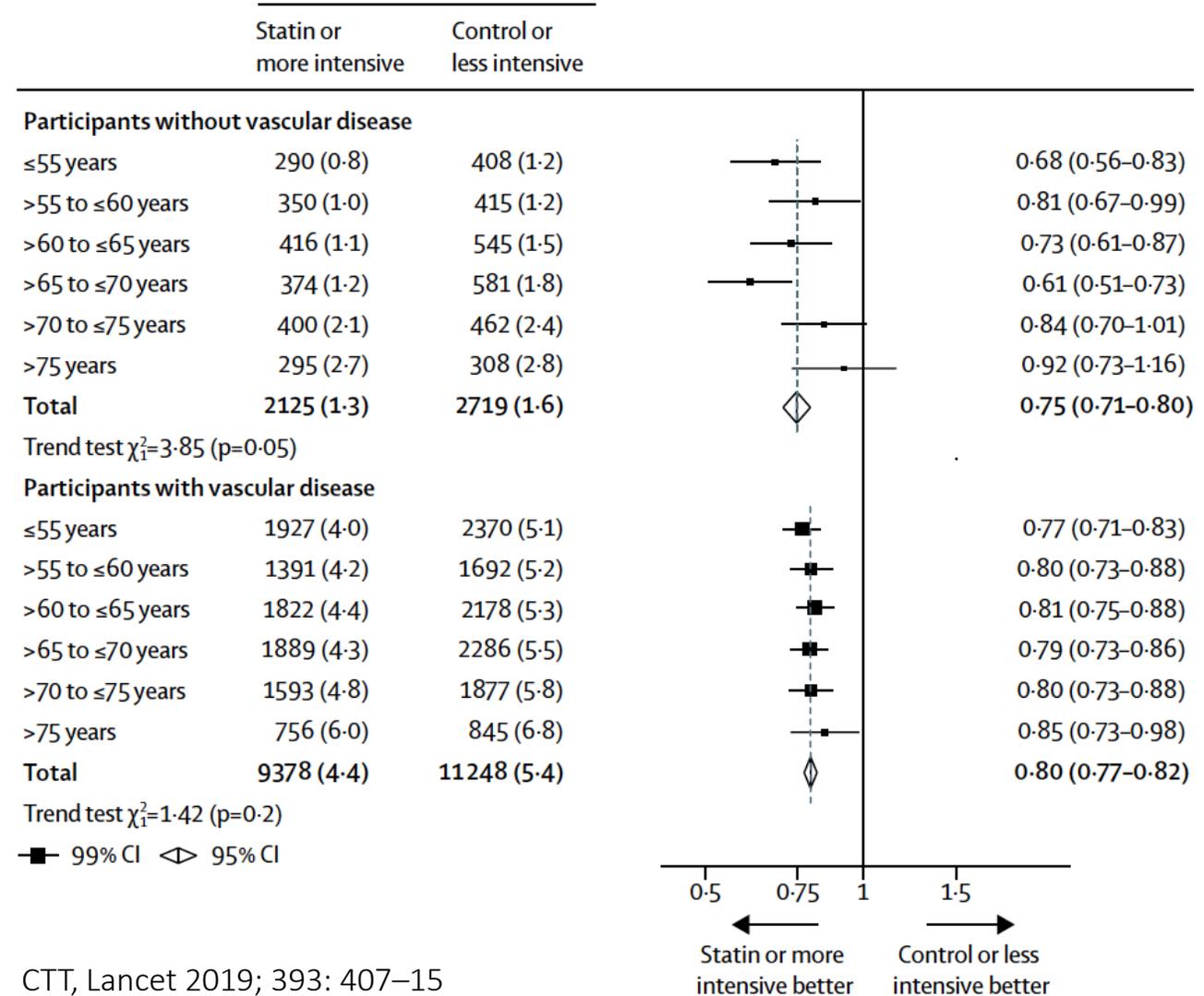
Treatment of hypercholesterolaemia in older adults calls for a patient-centred approach

Kleipool EEF, et al. Heart 2020;106:261–266.

Determinanti del successo (o dell'insuccesso...) terapeutico

➢ Inadeguata aderenza da parte del paziente alle prescrizioni terapeutiche
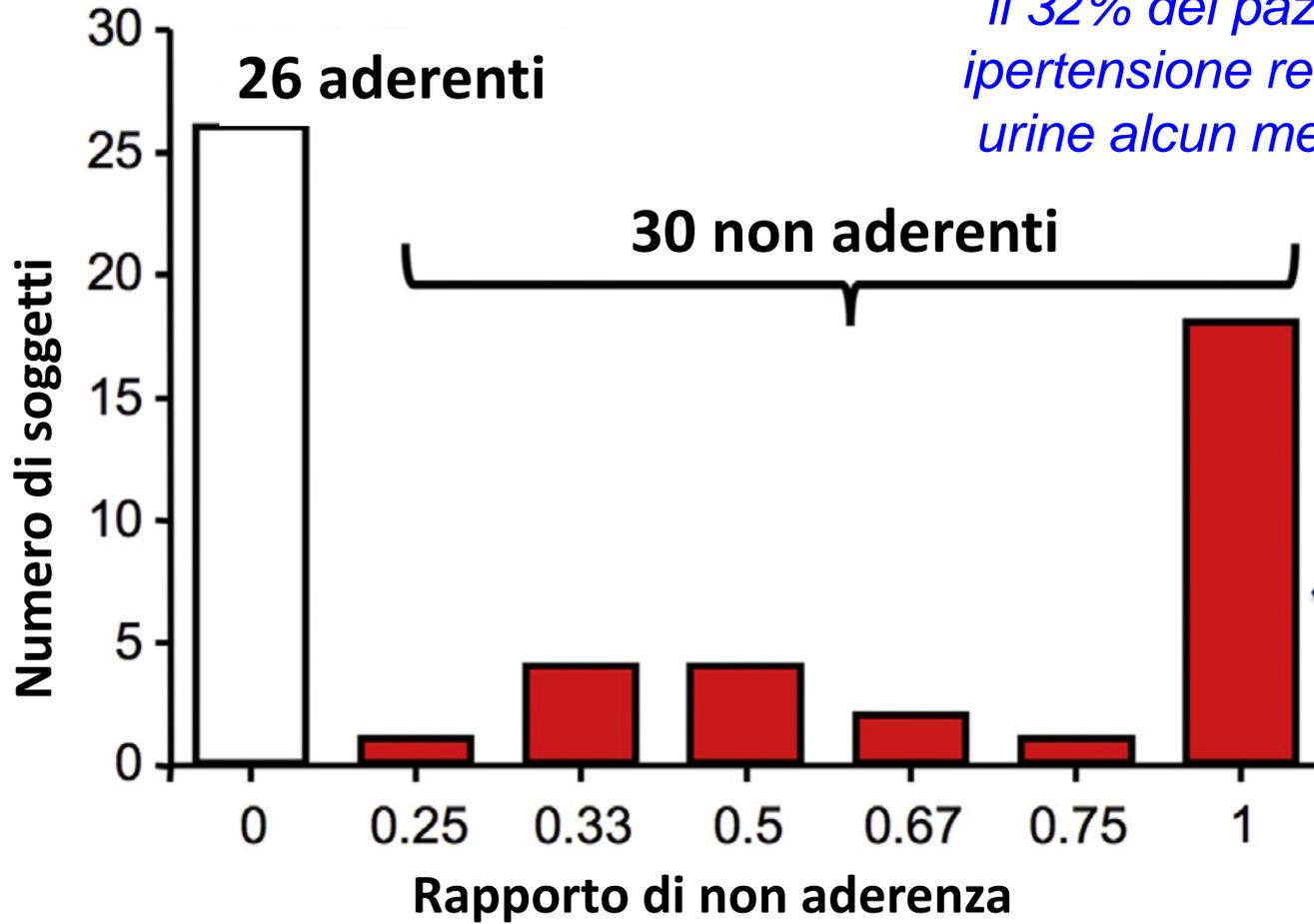
Brinker S et al., J Am Coll Cardiol. 2014; 63(8):834-5
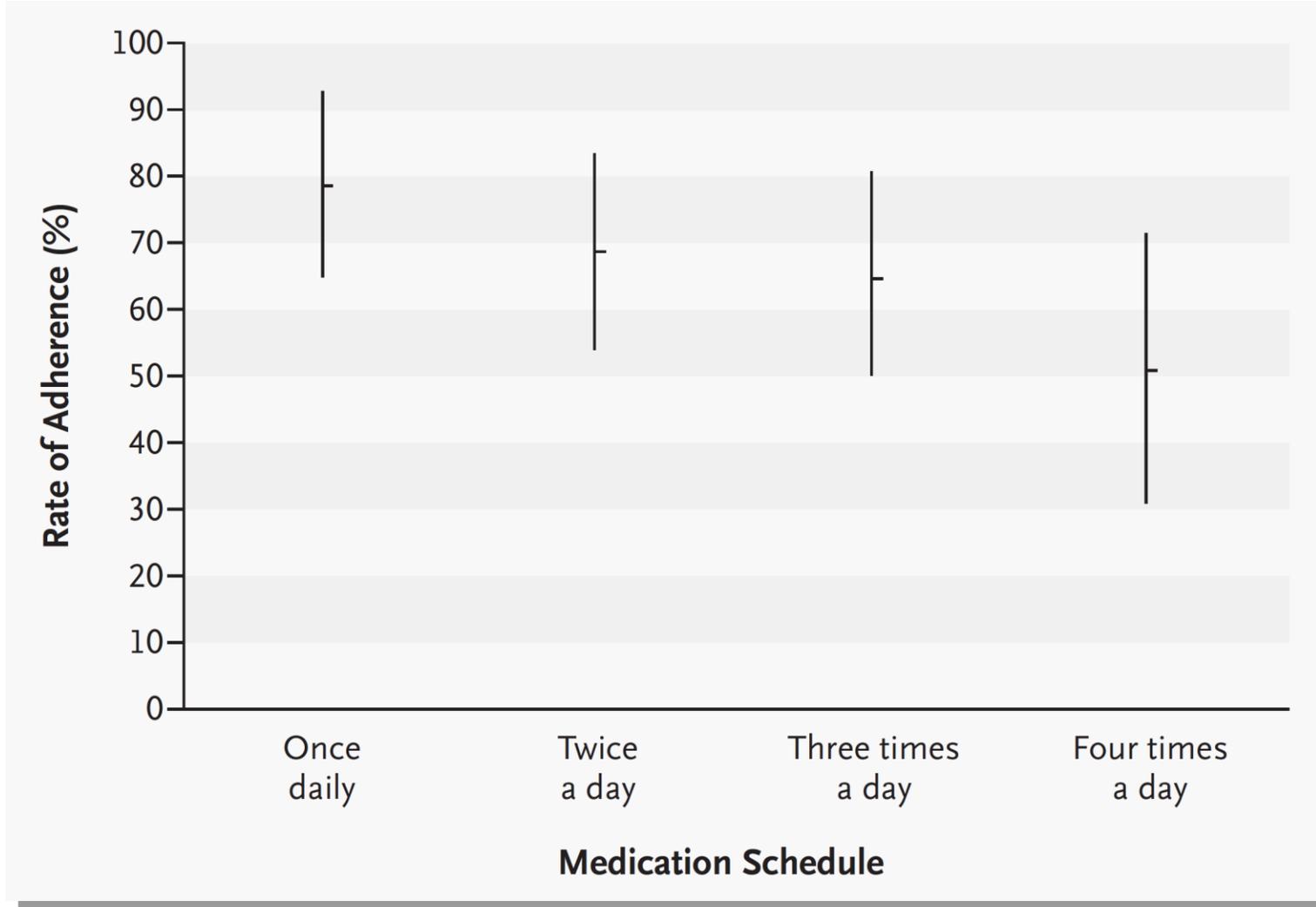
Aderenza al farmaco in base alla frequenza delle dosi

Claxton AJ et al. Clin Ther 2001;23:1296-310

Distribuzione degli utilizzatori nella popolazione di età ≥65 anni per numero di sostanze diverse

L'uso del farmaci in Italia – OSMED 2017
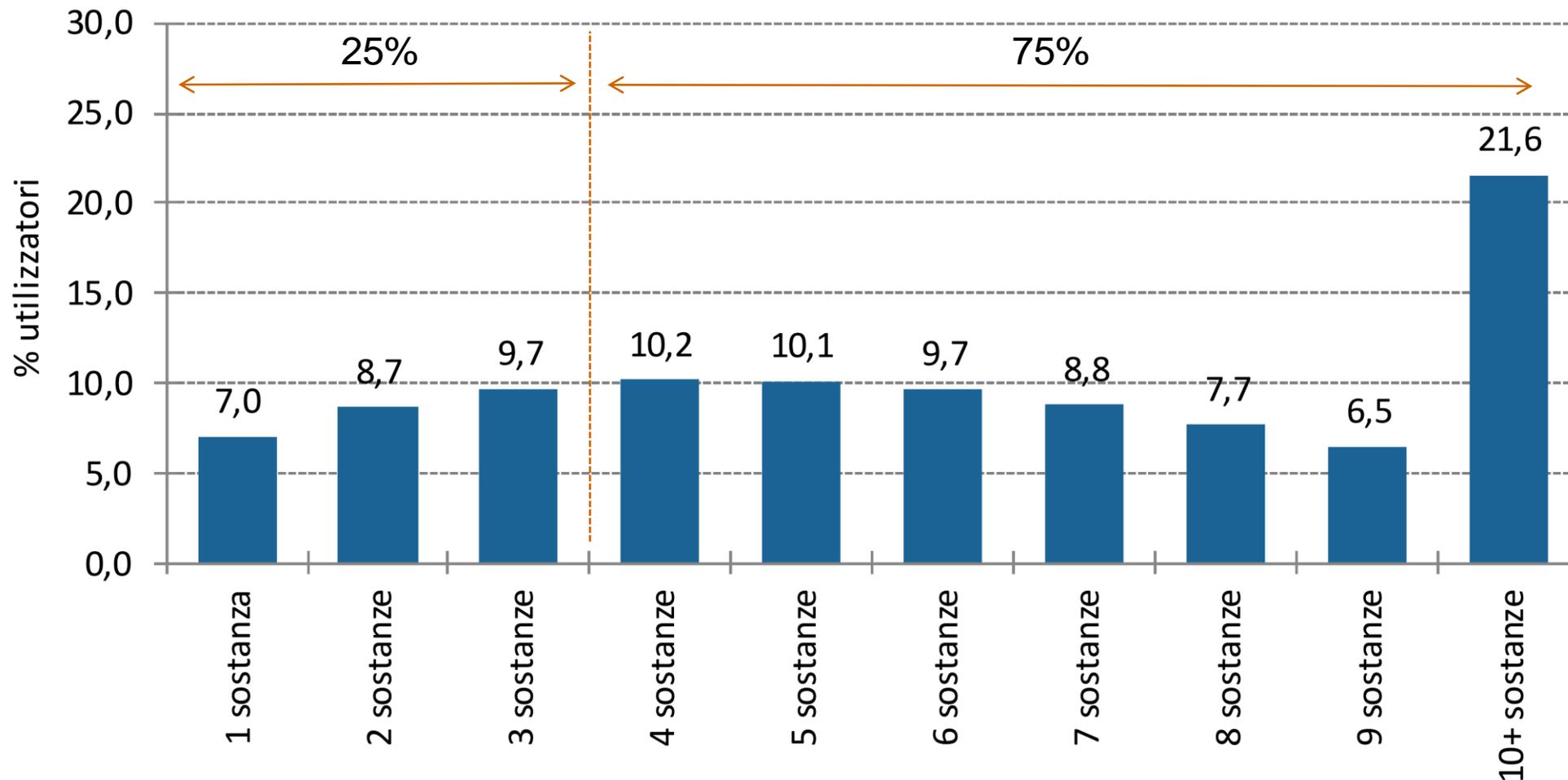
Temporal trends in comorbidities among patients diagnosed with incident heart failure, from 2002 to 2014

Conrad N et al. Lancet 2018; 391: 572–80
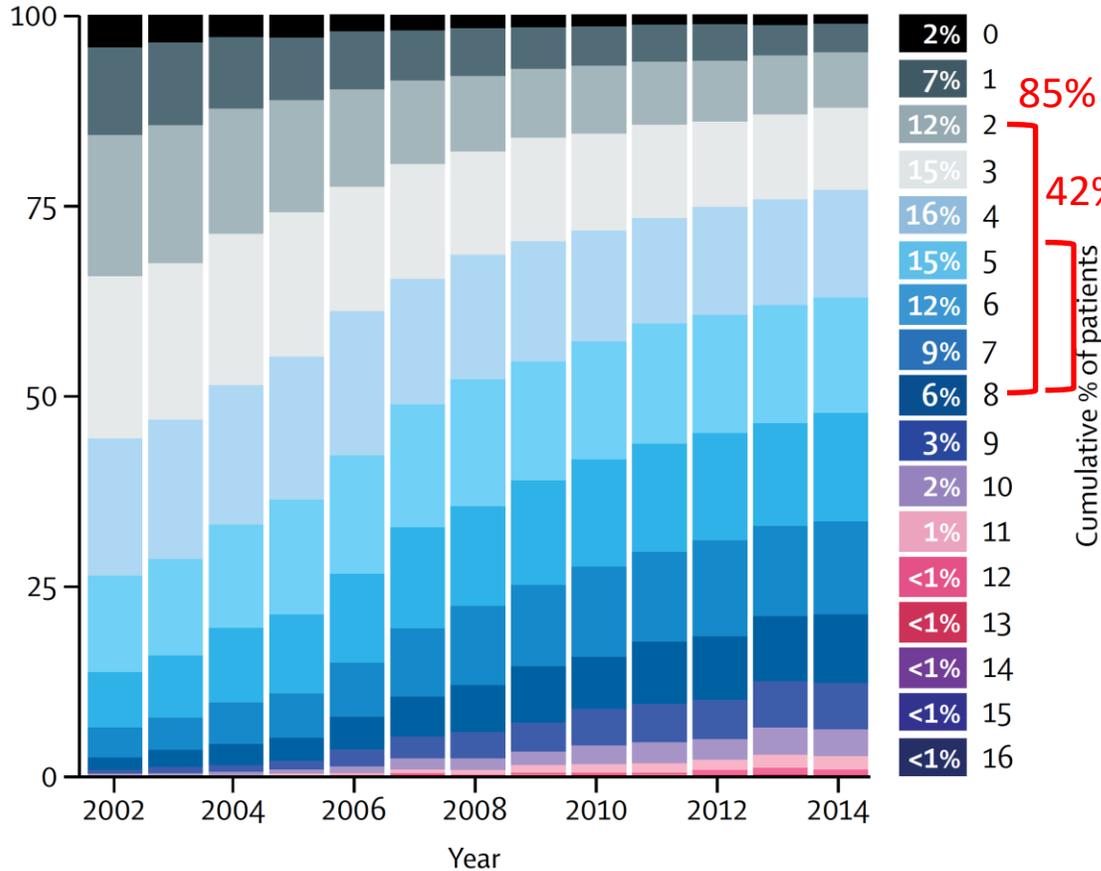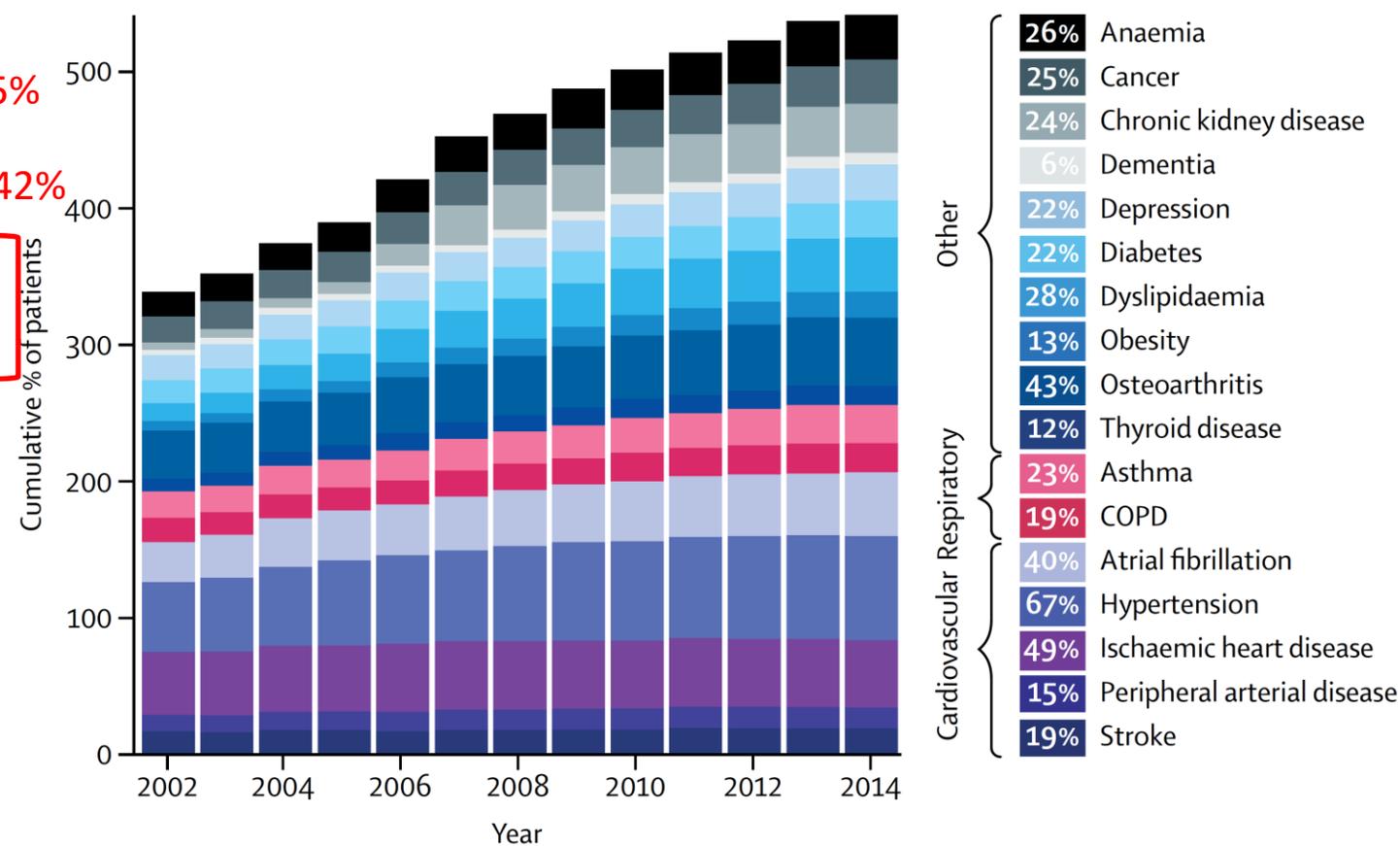
Clinical Practice Guidelines and Quality of Care for Older Patients With Multiple Comorbid Disease
Implications for Pay for Performance

The patient would take 12 separate medications with a medication complexity score of 14. This regimen requires 19 doses per day, taken at 5 times during a typical day, assuming that albuterol "as needed" is taken twice daily, plus weekly alendronate.

SOUNDING BOARD

Potential Pitfalls of Disease-Specific Guidelines for Patients with Multiple Conditions
Mary E. Tinetti, M.D., Sidney T. Bogardus, Jr., M.D., and Joseph V. Agostini, M.D.

Treatment Regimen Based on Clinical Practice Guidelines for a Hypothetical 79-Year-Old Woman With Hypertension, Diabetes Mellitus, Osteoporosis, Osteoarthritis, and COPD*

Time	Medications†	Other
7:00 AM	Ipratropium metered dose inhaler 70 mg/wk of alendronate	Check feet Sit upright for 30 min on day when alendronate is taken Check blood sugar
8:00 AM	500 mg of calcium and 200 IU of vitamin D 12.5 mg of hydrochlorothiazide 40 mg of lisinopril 10 mg of glyburide 81 mg of aspirin 850 mg of metformin 250 mg of naproxen 20 mg of omeprazole	Eat breakfast 2.4 g/d of sodium 90 mmol/d of potassium Low intake of dietary saturated fat and cholesterol Adequate intake of magnesium and calcium Medical nutrition therapy for diabetes‡ DASH‡
2:00 PM		Eat lunch 2.4 g/d of sodium 90 mmol/d of potassium Low intake of dietary saturated fat and cholesterol Adequate intake of magnesium and calcium Medical nutrition therapy for diabetes‡ DASH‡
1:00 PM	Ipratropium metered dose inhaler 500 mg of calcium and 200 IU of vitamin D	
7:00 PM	Ipratropium metered dose inhaler 850 mg of metformin 500 mg of calcium and 200 IU of vitamin D 40 mg of lovastatin 250 mg of naproxen	Eat dinner 2.4 g/d of sodium 90 mmol/d of potassium Low intake of dietary saturated fat and cholesterol Adequate intake of magnesium and calcium Medical nutrition therapy for diabetes‡ DASH‡
11:00 PM	Ipratropium metered dose inhaler	
As needed	Albuterol metered dose inhaler	

Determinanti del successo
(o dell'insuccesso...) terapeutico

➢ Scelte terapeutiche non (completamente) adeguate al raggiungimento dei target raccomandati dalla linee guida

# General BP lowering strategy in patients with Hypertension.
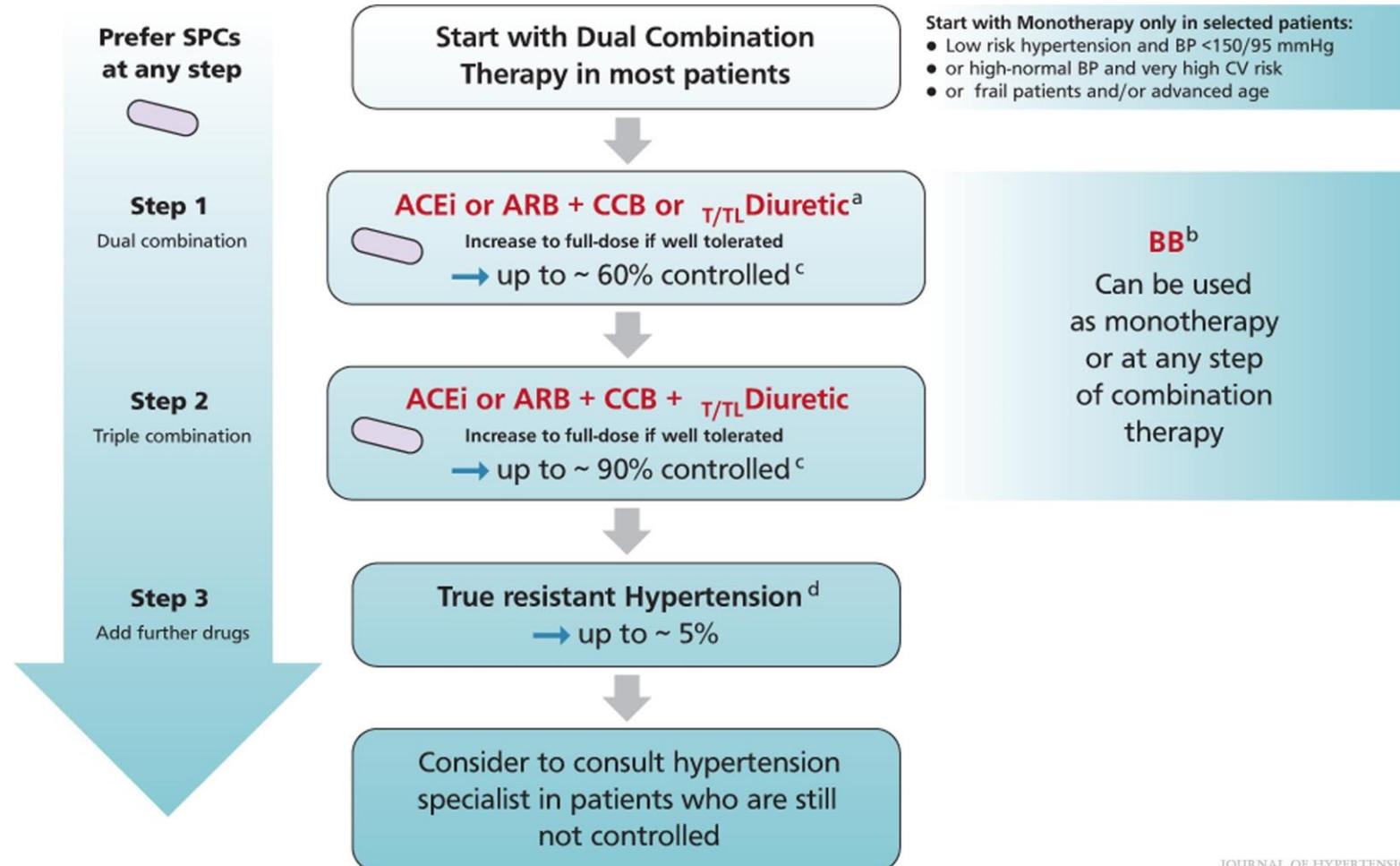
La riduzione pressoria incrementale che si ottiene combinando 2 classi di antipertensivi è 5 volte superiore a quello ottenibile raddoppiando la dose di un singolo farmaco


Wald et al. Am J Med 2009;122:290-300.
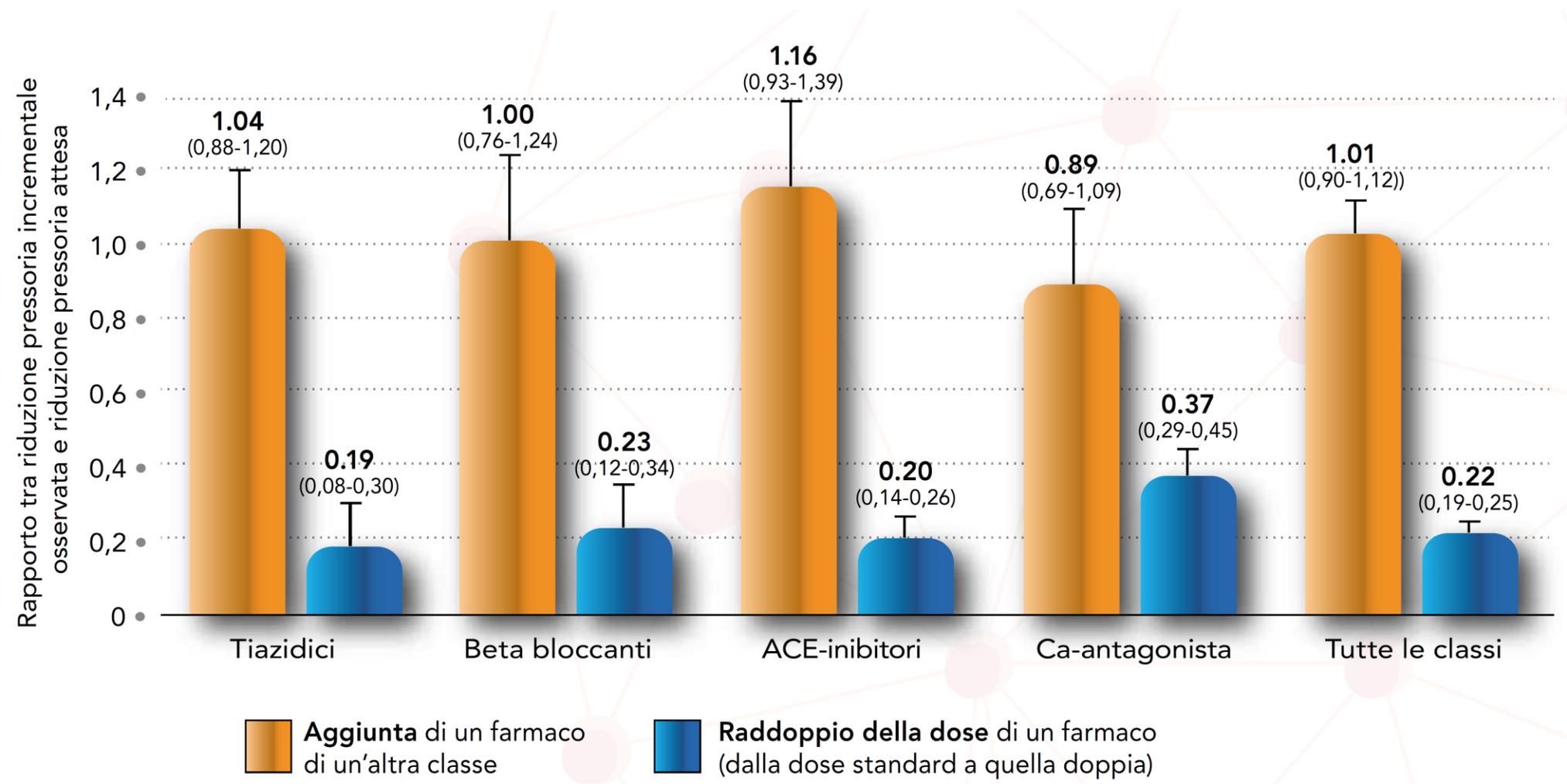
Reciprocal action mechanism of inhibitors of angiotensin renin system diuretics and calcium channel blockers
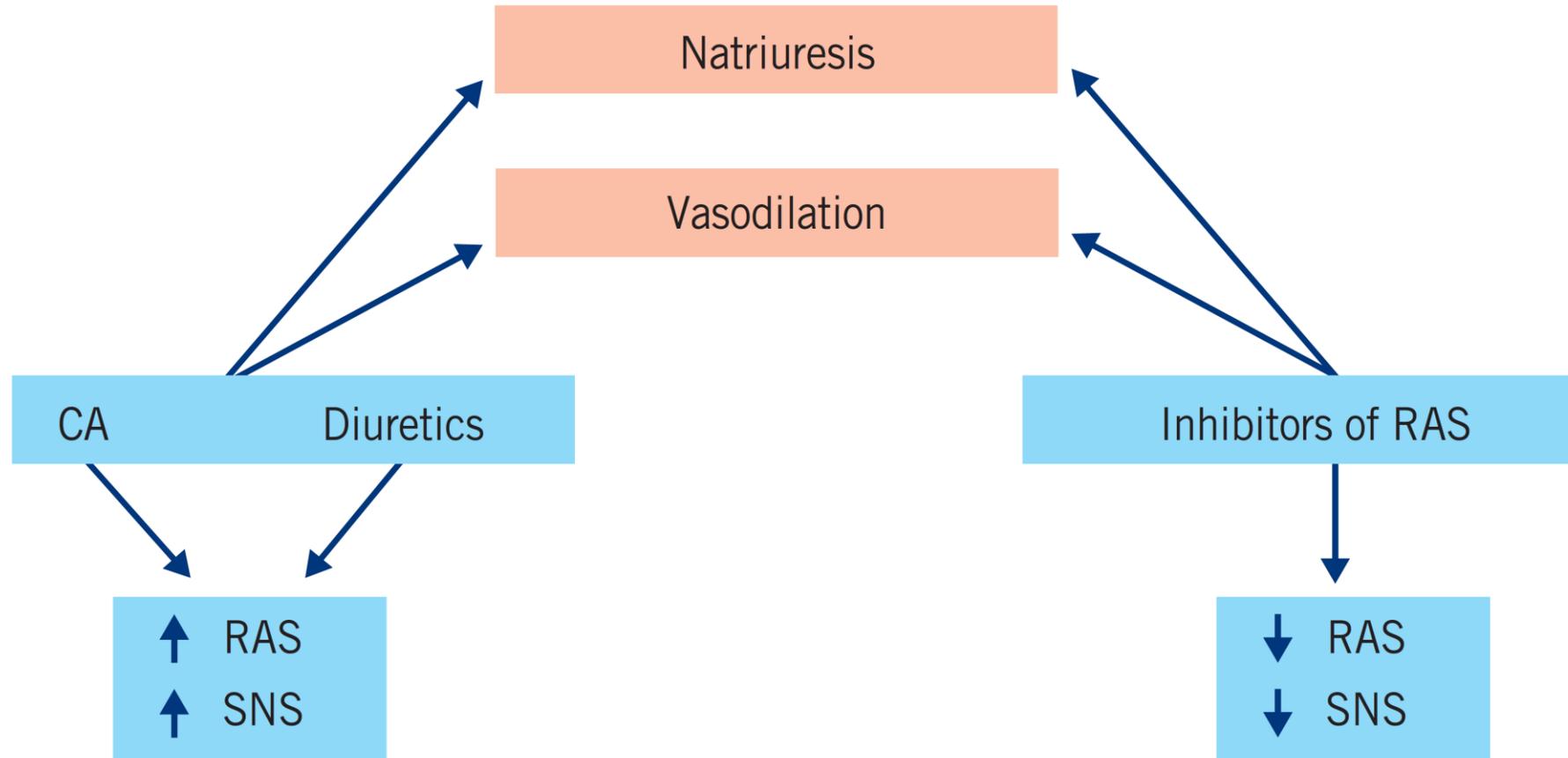
CA: Calcium channel blockers; RAS: Renin angiotensin system; SNS: Sympathetic nervous system

Severe PS et al. European Heart Journal 2011;32, 2499-2506.
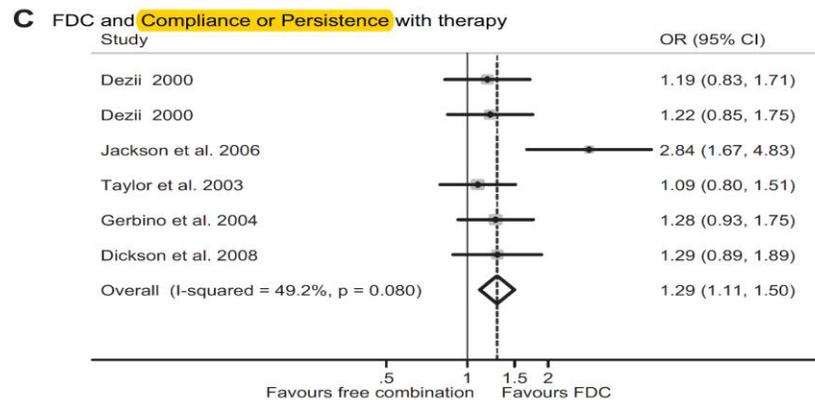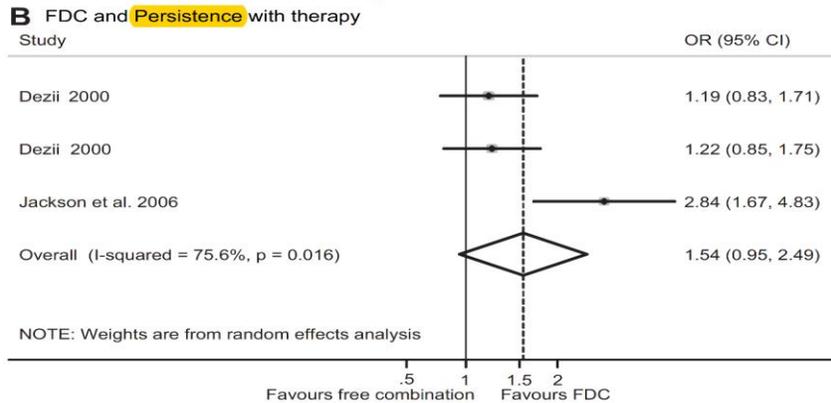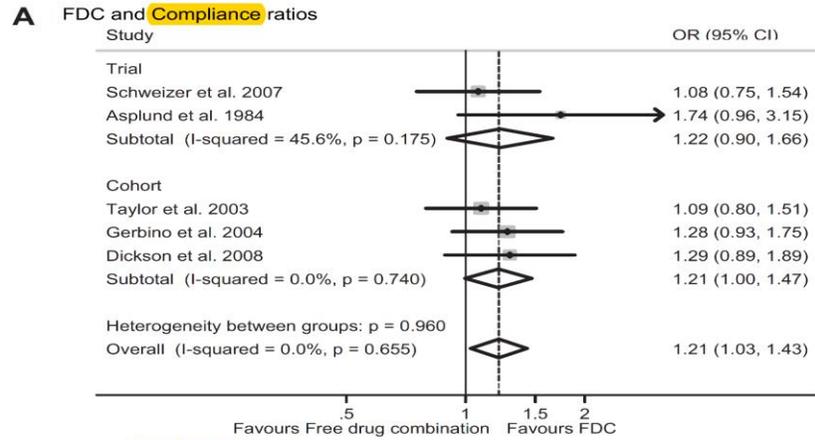
Antihypertensive Agents, Compliance

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

Ajay K. Gupta, Shazia Arshad, Neil R. Poulter
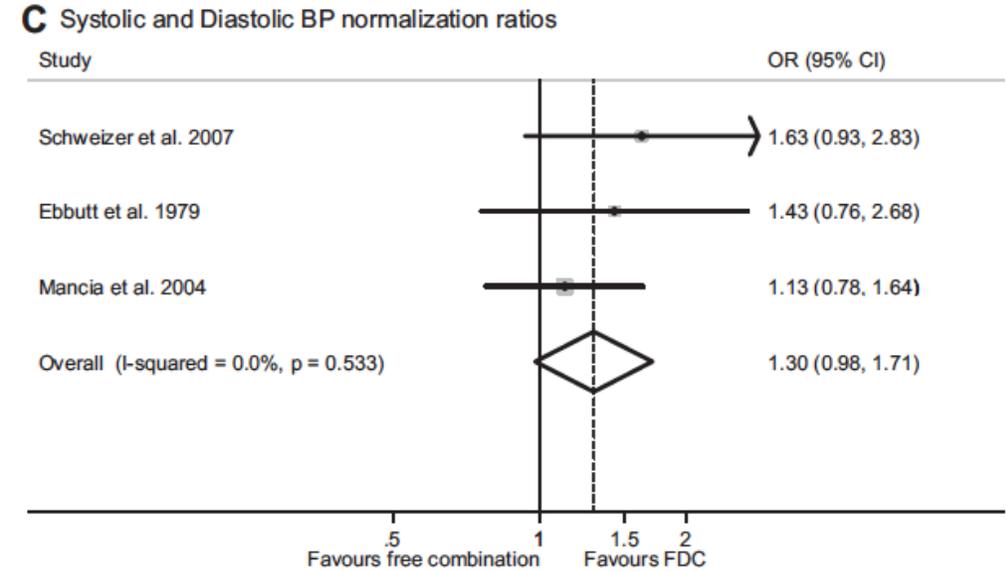
…In conclusion, compared with free-drug combinations, FDCs of antihypertensive agents are associated with a **significant improvement in compliance** and with nonsignificant beneficial trends in BP and adverse effects.

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

Complementary mechanism of action of Statins and Ezetimibe on lipid profile
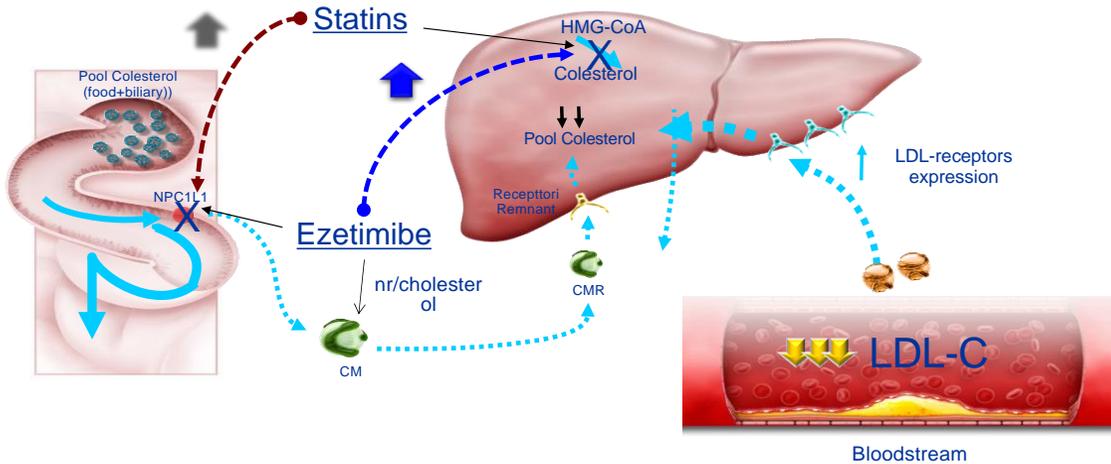
NPC1L1 = Niemann-Pick C1-like 1;
HMG-CoA = 3-hydroxy-3-methylglutaryl acetyl coenzyme A;
CMR = chylomicron remnant.
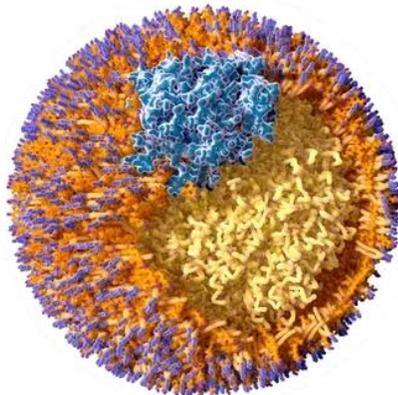
Grigore L et al. Vas Health Risk Manag. 2008;4:267–278
Mach F et al. European Heart Journal (2020) 41, 111188

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Intensity of lipid lowering treatment

| Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%

Effect of Simvastatin-Ezetimibe Compared With Simvastatin Monotherapy After Acute Coronary Syndrome Among Patients 75 Years or Older - A Secondary Analysis of a Randomized Clinical Trial

A Primary composite efficacy end point
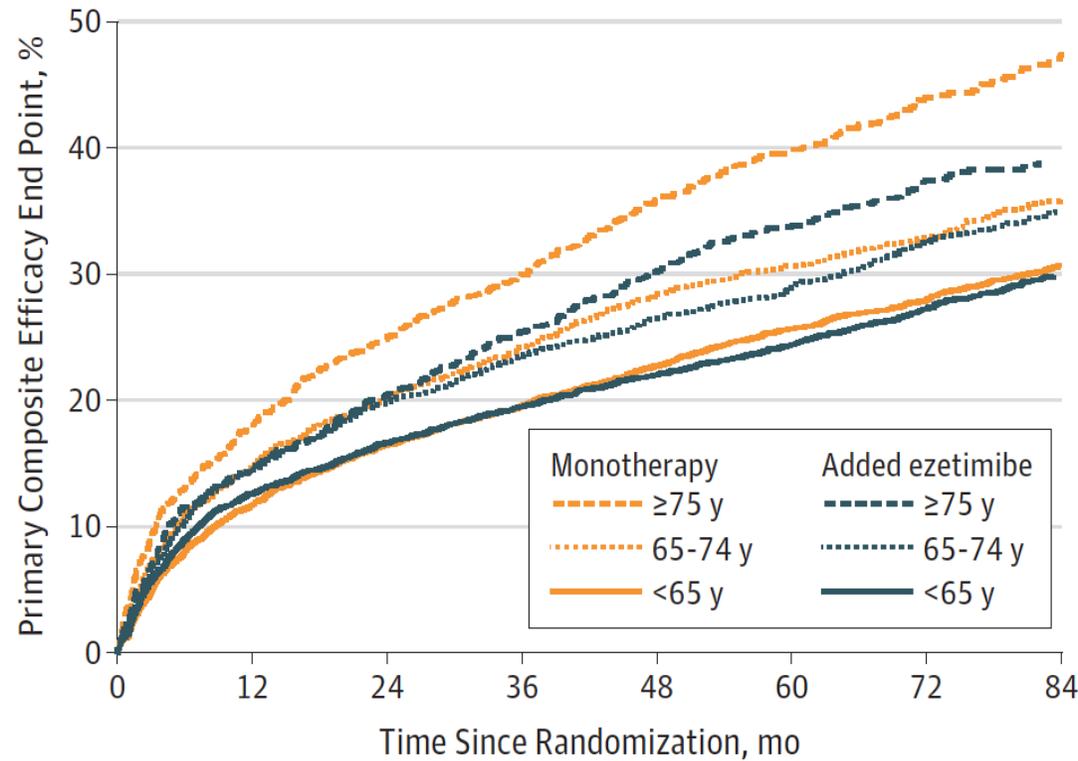
B CVD death, MI, and stroke
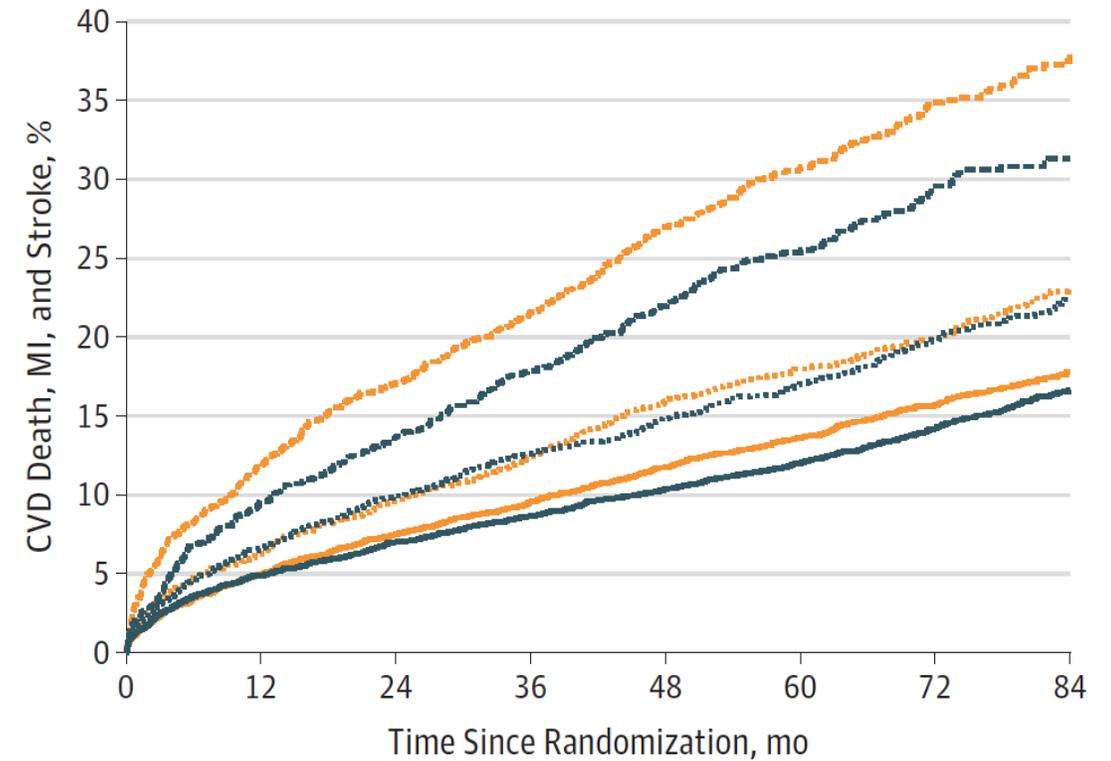
Adherence to Lipid-Lowering Treatment by Single-Pill Combination of Statin and Ezetimibe

PDC >75%: highly adherent
PDC <25%: poorly adherent
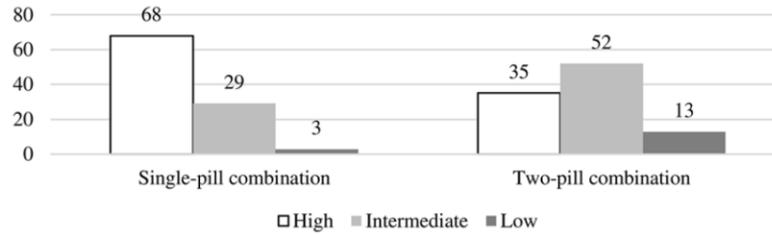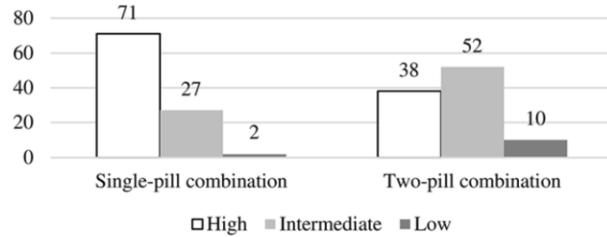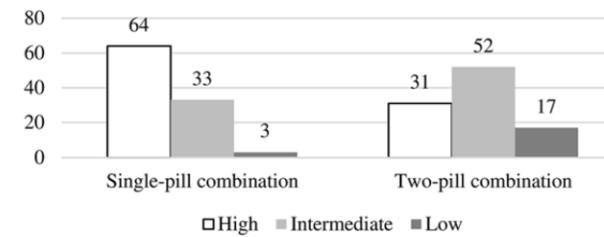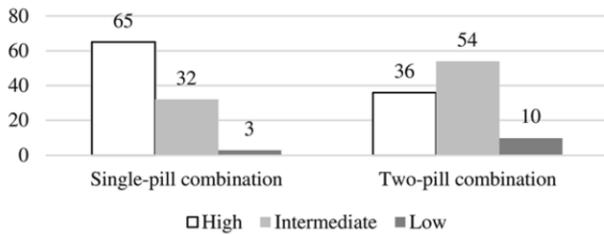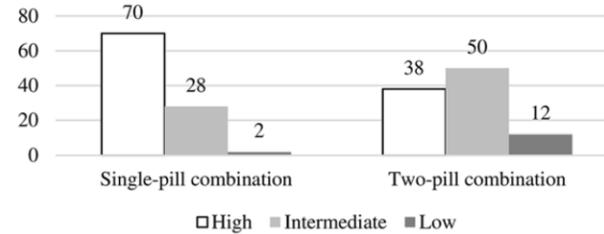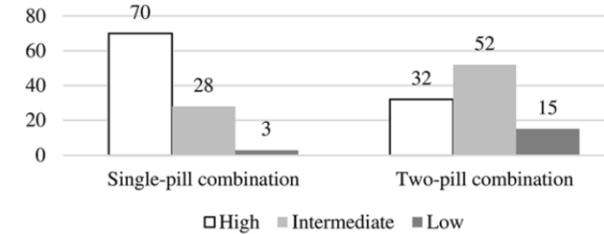
Rea F et al. Adv Ther (2021) 38:5270–5285

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E GERIATRIA
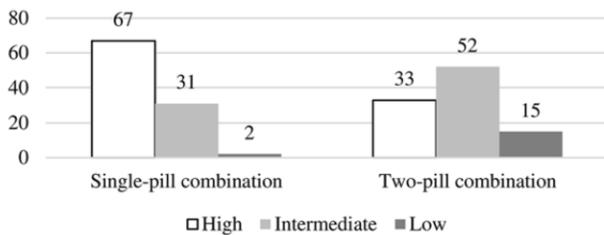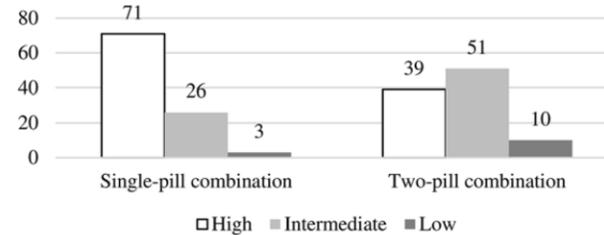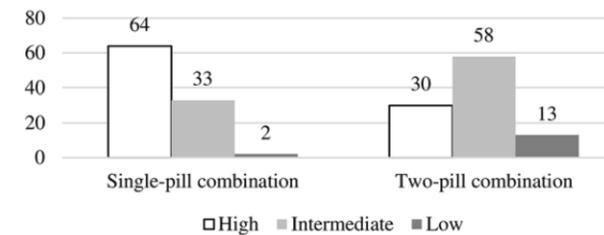
Sir Nicholas John Wald

Polipillola: una strategia per ridurre gli eventi cardiovascolari di più dell'80%

Fattore di rischio	Componente	Riduzione del fattore di rischio	Riduzione del rischio di IHD	Eventi IHD in assenza di trattamento
Colesterolo LDL	Statina	70 mg/dl	61%	100
				39 residuo
Pressione arteriosa	Mezza dose standard di: Diuretico β bloccante Inibitore RAS	10.7 mmHg diastolica	46%	21 residuo
Aggregazione piastrinica	ASA	-	32%	14 residuo
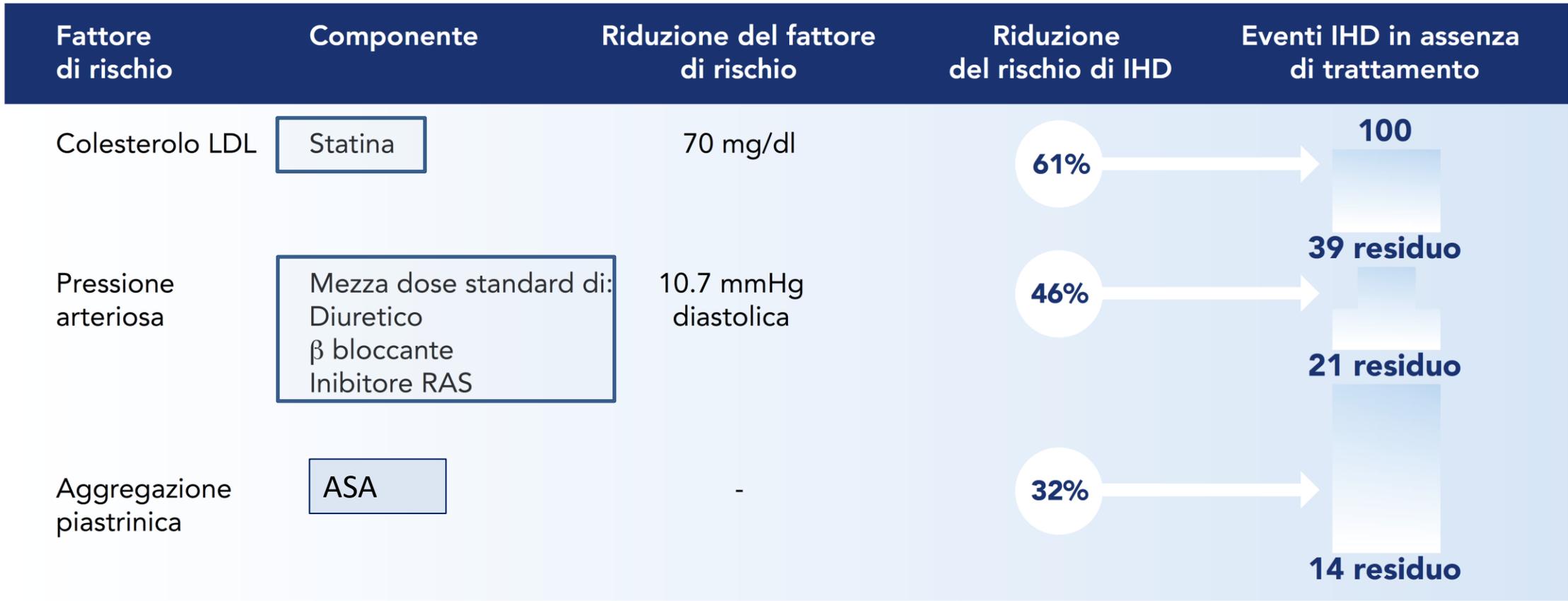
Effetto combinato 100-14= 86% prevenuti

Wald NJ, Law MR. . BMJ. 2003 Jun 28;326(7404):1419.

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

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*

A First Event of the Primary Outcome — Hazard ratio, 0.79 (95% CI, 0.63–1.00)

B First and Recurrent Events of the Primary Outcome — Hazard ratio, 0.76 (95% CI, 0.60–0.97)
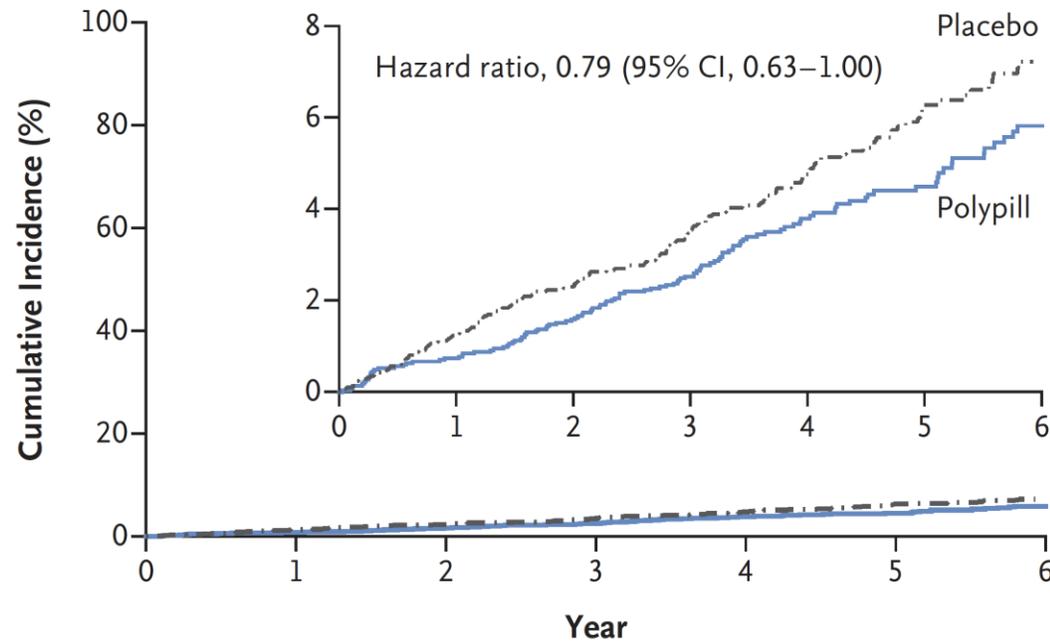
No. at Risk (A)

Placebo	2852	2781	2725	2499	1552	984	634
Polypill	2861	2814	2759	2536	1581	1020	676
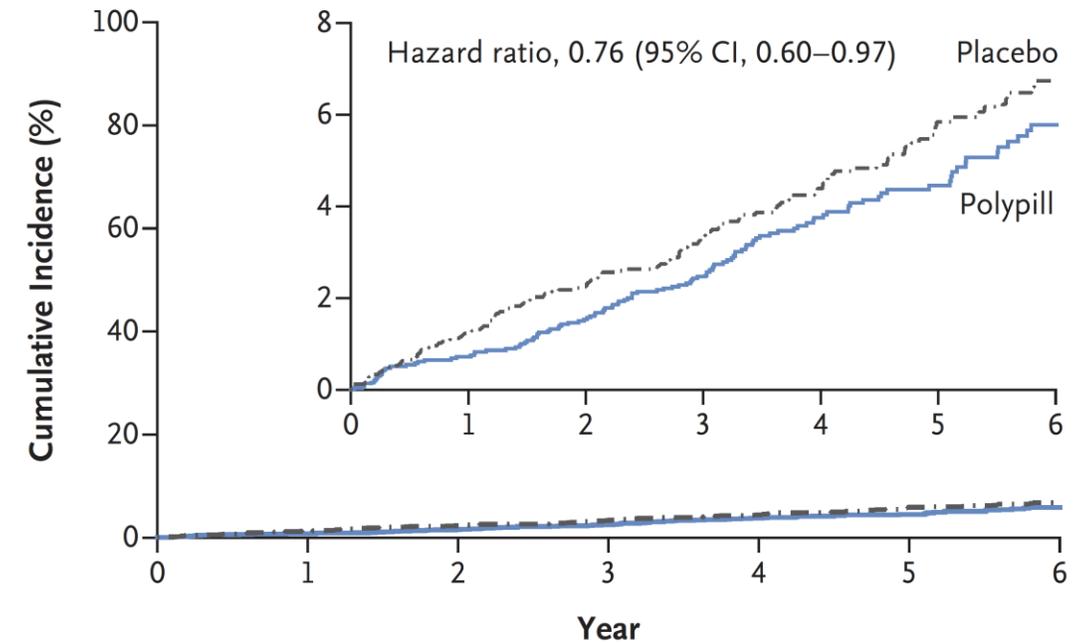
No. at Risk (B)

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

Yusuf S et al. N Engl J Med 2021;384:216-28.

Synergy between atorvastatin, amlodipine and perindopril for CV 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

Left graph legend:
— Atorvastatin/Amlodipine±Perindopril
— Placebo/Amlodipine±Perindopril

Y-axis: Cumulative incidence for non-fatal myocardial infarction and fatal coronary heart disease (%)
X-axis: Time (years)

-53%

HR=0.47, CI 0.32-0.69, p<0.001, ARR=1.6%

Right graph legend:
— Atorvastatin/Atenolol±Thiazide type
— Placebo/Atenolol±Thiazide type

Y-axis: Cumulative incidence for non-fatal myocardial infarction and fatal coronary heart disease (%)
X-axis: Time (years)

-16% NS

HR=0.84, CI 0.60-1.17, p=0.30, ARR=10.5%

*"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 "*

Endpoint	Risk ration (95% CI)		
CV mortality, nonfatal MI and stroke	0.58 (0.40 to 0.85)		-42%
Nonfatal MI, fatal CHD and coronary revascularization	0.61 (0.38 to 0.97)		-39%
Total CV events and procedures	0.76 (0.59 to 0.97)		-24%

0   0.5   1   1.5

Atorvastatin/amlodipine/perindopril **better**   *Atorvastatin/atenolol/thiazide* **better**

Sever et al. Eur Heart J. 2006;27:2982-2988.

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Polypill Strategy in Secondary Cardiovascular Prevention

J.M. Castellano, S.J. Pocock, D.L. Bhatt, A.J. Quesada, R. Owen, A. Fernandez-Ortiz, P.L. Sanchez, F. Marin Ortuño, J.M. Vazquez Rodriguez, A. Domingo-Fernández, I. Lozano, M.C. Roncaglioni, M. Baviera, A. Foresta, L. Ojeda-Fernandez, F. Colivicchi, S.A. Di Fusco, W. Doehner, A. Meyer, F. Schiele, F. Ecarnot, A. Linhart, J.-C. Lubanda, G. Barczi, B. Merkely, P. Ponikowski, M. Kasprzak, J.M. Fernandez Alvira, V. Andres, H. Bueno, T. Collier, F. Van de Werf, P. Perel, M. Rodriguez-Manero, A. Alonso Garcia, M. Proietti, M.M. Schoos, T. Simon, J. Fernandez Ferro, N. Lopez, E. Beghi, Y. Bejot, D. Vivas, A. Cordero, B. Ibañez, and V. Fuster, for the SECURE Investigators*

N=2500 Post MI >65

ASA 100
ATORVASTATIN 20/40
RAMIPRIL 2.5/5/10

+ At Least One

a. Documented DM
b. Mild to moderate CKD
c. Prior MI
d. Prior coronary revascularization
e. Prior stroke
f. Age ≥ 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.

Demographic Characteristics of the Patients at Baseline.*

Characteristic	Polypill Group (N = 1237)	Usual-Care Group (N = 1229)
Age		
Mean — yr	75.8±6.7	76.1±6.5
Distribution — no. (%)		
<75 yr	516 (41.7)	482 (39.2)
≥75 yr	721 (58.3)	747 (60.8)

Cardiovascular Death, Nonfatal MI, Nonfatal Ischemic Stroke, or Urgent Coronary Revascularization at 3 Yr

HR, 0.76 (95% CI, 0.60–0.96); P=0.02 for superiority

Polypill: 9.5
Usual Care: 12.7
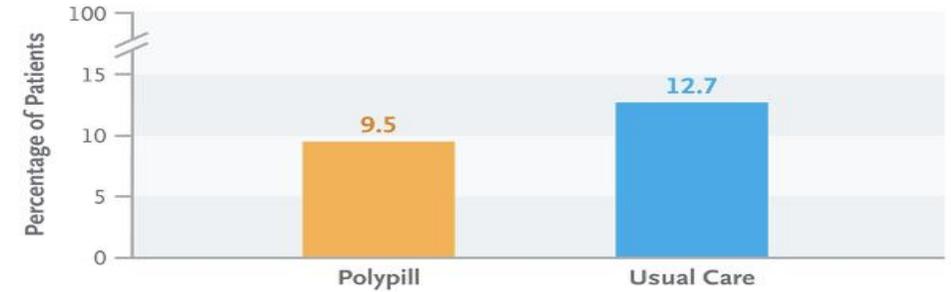
Cardiovascular Death, Nonfatal MI, or Nonfatal Ischemic Stroke at 3 Yr (Secondary Outcome)

HR, 0.70 (95% CI, 0.54–0.90); P=0.005

Polypill: 8.2
Usual Care: 11.7
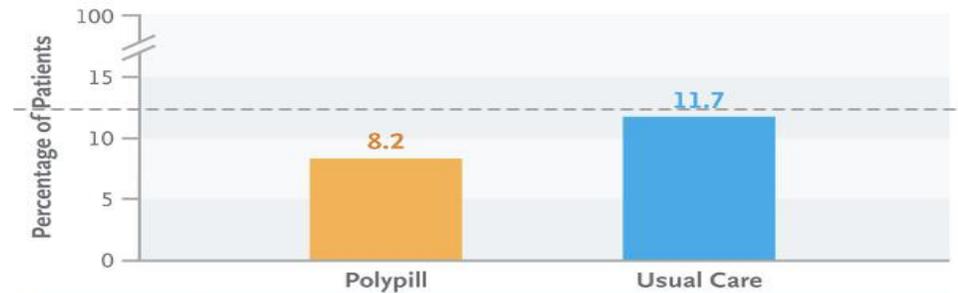
Medication Adherence as Reported by the Patients

Polypill   Usual Care

6 Months — Polypill: 70.6, Usual Care: 62.7
24 Months — Polypill: 74.1, Usual Care: 63.2

Polypill-based strategy vs. usual care for secondary prevention of CVD: a meta-analysis of RCTs
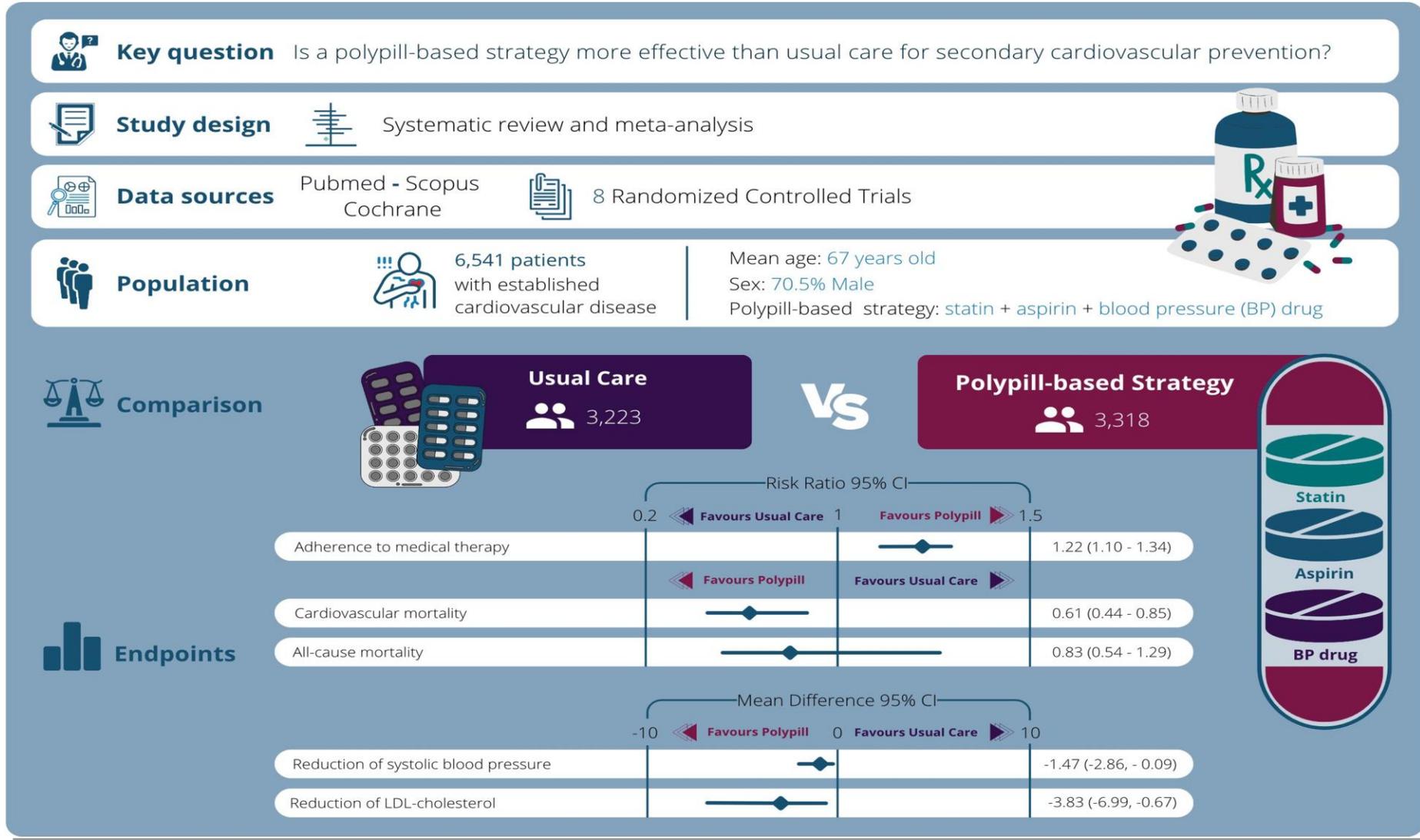
The polypill in cardiovascular prevention: evidence, limitations and perspective – position paper of the European Society of Hypertension

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

. **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)

2023 ESH Guidelines for the management of arterial hypertension

Use of a polypill containing two BP lowering drugs and a statin for LDL cholesterol lowering can be considered in hypertensive patients for primary prevention.	II	A

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

✧ Synergy

✧ Simplification

✧ Deprescription

Anticoagulant Use for Atrial Fibrillation Among Persons With Advanced Dementia at the End of Life

Characteristic	No. (%)		Adjusted OR (95% CI)	
	Anticoagulation in the last 6 mo of life (n = 5033)	No anticoagulation in the last 6 mo of life (n = 10 184)		
>1 y in nursing home	2154 (42.8)	2399 (23.6)	2.68 (2.48-2.89)	*
CHA_2DS_2VASC score[b]				
<4	681 (13.5)	1661 (16.3)	1 [Reference]	
5-6	1914 (38.0)	4242 (41.7)	1.10 (0.99-1.23)	
>7	2438 (48.4)	4281 (42.0)	1.38 (1.23-1.54)	*
ATRIA score[c]				
<3	796 (15.8)	2205 (21.7)	1 [Reference]	
4-6	1690 (33.6)	3584 (35.2)	1.19 (1.07-1.32)	
>7	2547 (50.6)	4395 (43.2)	1.25 (1.13-1.39)	*
Other clinical factors				
Rejection of care	454 (9.0)	844 (8.3)	1.03 (0.91-1.17)	
Falls	1690 (33.6)	3214 (31.6)	1.04 (0.96-1.12)	
Weight loss	1856 (37.0)	3363 (33.5)	1.09 (1.01-1.18)	*
Pressure ulcer	2052 (40.8)	3228 (31.7)	1.37 (1.27-1.48)	*
Difficulty swallowing	1136 (22.6)	2008 (19.8)	1.12 (1.02-1.22)	*
Restraint use	189 (3.8)	433 (4.3)	0.79 (0.66-0.95)	
Hospice use	1296 (25.8)	3375 (33.1)	0.76 (0.70-0.83)	*

Among 15.217 nursing home residents with AF and advanced dementia (mean age, 87.5±6.76 years, 68.2% women), **5033 (33.1%) received an anticoagulant in the last 6 months of life.**

Ouellet GM et al. JAMA Intern Med. 2021

Systolic Blood Pressure and Mortality in Community-Dwelling Older Adults: Frailty as an Effect Modifier - ActiFE Study Group

Splines for the association between systolic blood pressure and 8-y all-cause mortality stratified by frailty.
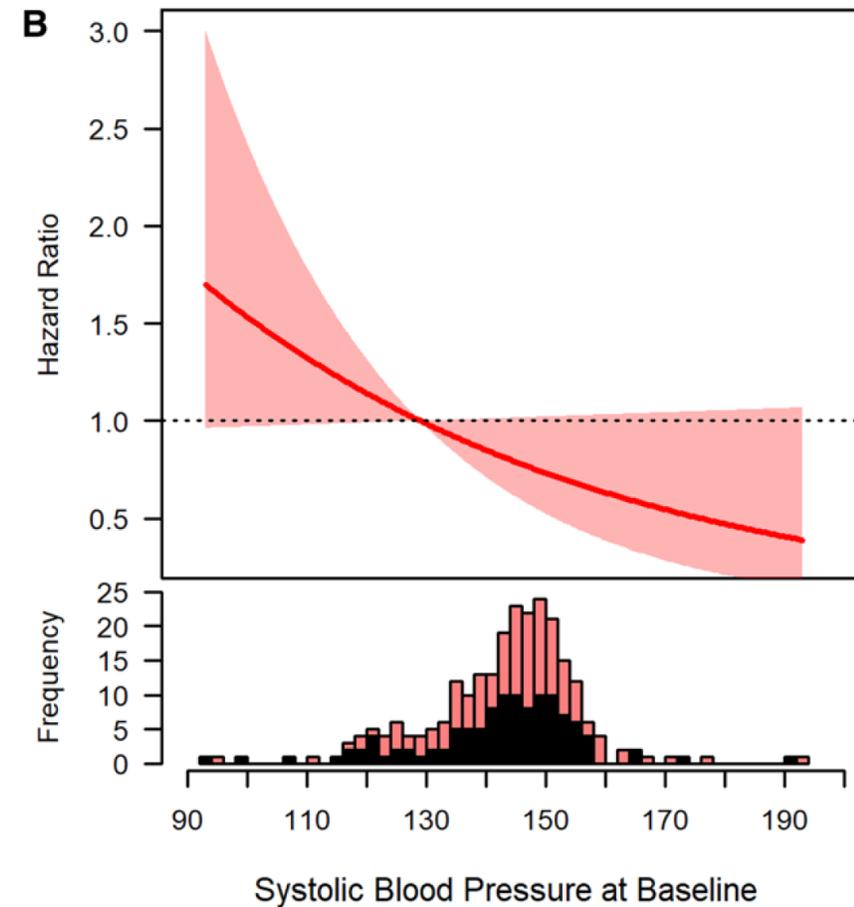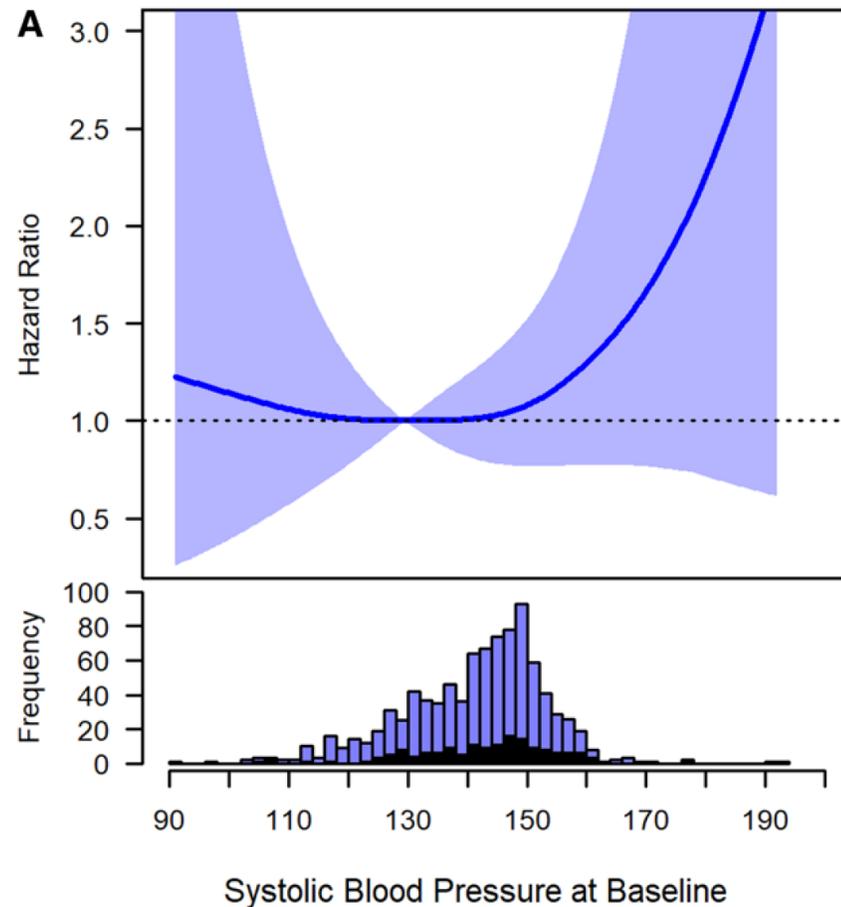
Effect of Antihypertensive Medication Reduction vs Usual Care on Short-term Blood Pressure Control in Patients With Hypertension Aged 80 Years and OlderThe OPTIMISE RCT

Question Among older adults taking multiple antihypertensive medications, is a strategy of antihypertensive medication reduction noninferior to usual care with regard to short-term blood pressure control?

Patients: subjects who, **in opinion of their physicians**, might potentially benefit from medication reduction due to 1 or more of the following existing characteristics: **polypharmacy, comorbidity, nonadherence or dislike of medicines, or frailty.**

Safety and Benefit of Discontinuing Statin Therapy in the Setting of Advanced, Life-Limiting Illness

Kutner JS et al. JAMA Intern Med. 2015 May ; 175(5): 691–700

In 75-year-old primary prevention patients previously adherent to statin therapy for at least 2 years, discontinuation of statins was associated with an increased risk of admission for a cardiovascular event

CV effect of discontinuing statins for primary prevention at the age of 75 years: a nationwide population-based cohort study in France

Principal result

Hazard ratio 1.33 (95% CI, 1.18-1.50)

Statins discontinued

Statins continued

Adjusted Cumulative Incidence, %

Time since 75th birthday, months

Giral P et al. European Heart Journal (2019) 40, 3516–3525