IPERTENSIONE ARTERIOSA E COMORBIDITA'
I FARMACI ANTIPERTENSIVI DI PRIMA SCELTA
ED I TARGET TERAPEUTICI OTTIMALI

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Definitions and Classification of Office Blood Pressure Levels (mmHg)

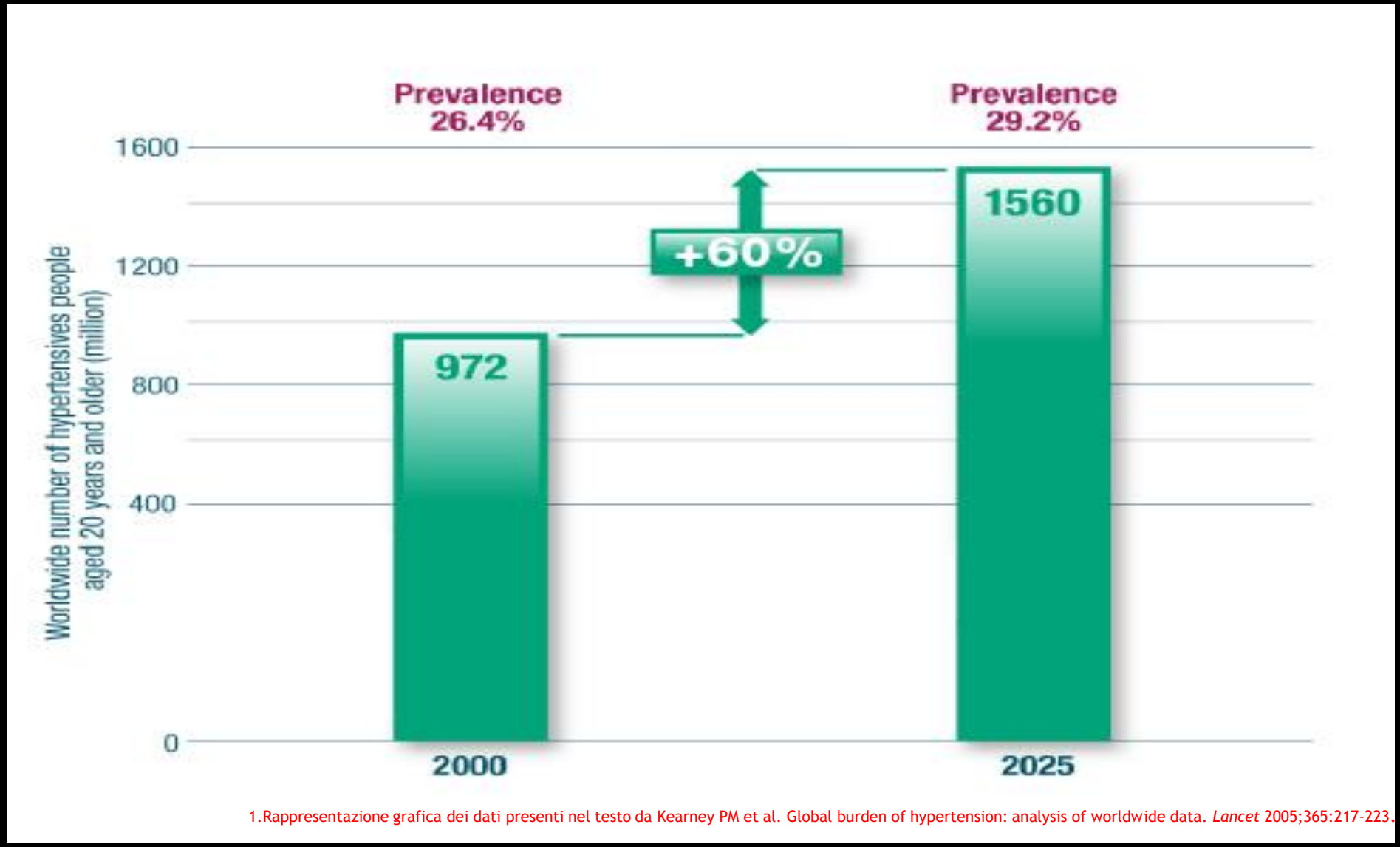
Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120 - 129	and/or	80 - 84
High normal	130 - 139	and/or	85 - 89
Grade 1 hypertension	140 - 159	and/or	90 - 99
Grade 2 hypertension	160 - 179	and/or	100 - 109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

The BP category is defined by the highest level of BP, whether systolic or diastolic.

L'organizzazione mondiale della sanità ha analizzato dati sulla ipertensione arteriosa e ha visto che livelli pressori non ottimali sono responsabili del 62% degli eventi cardiovascolari e del 49% degli eventi ischemici

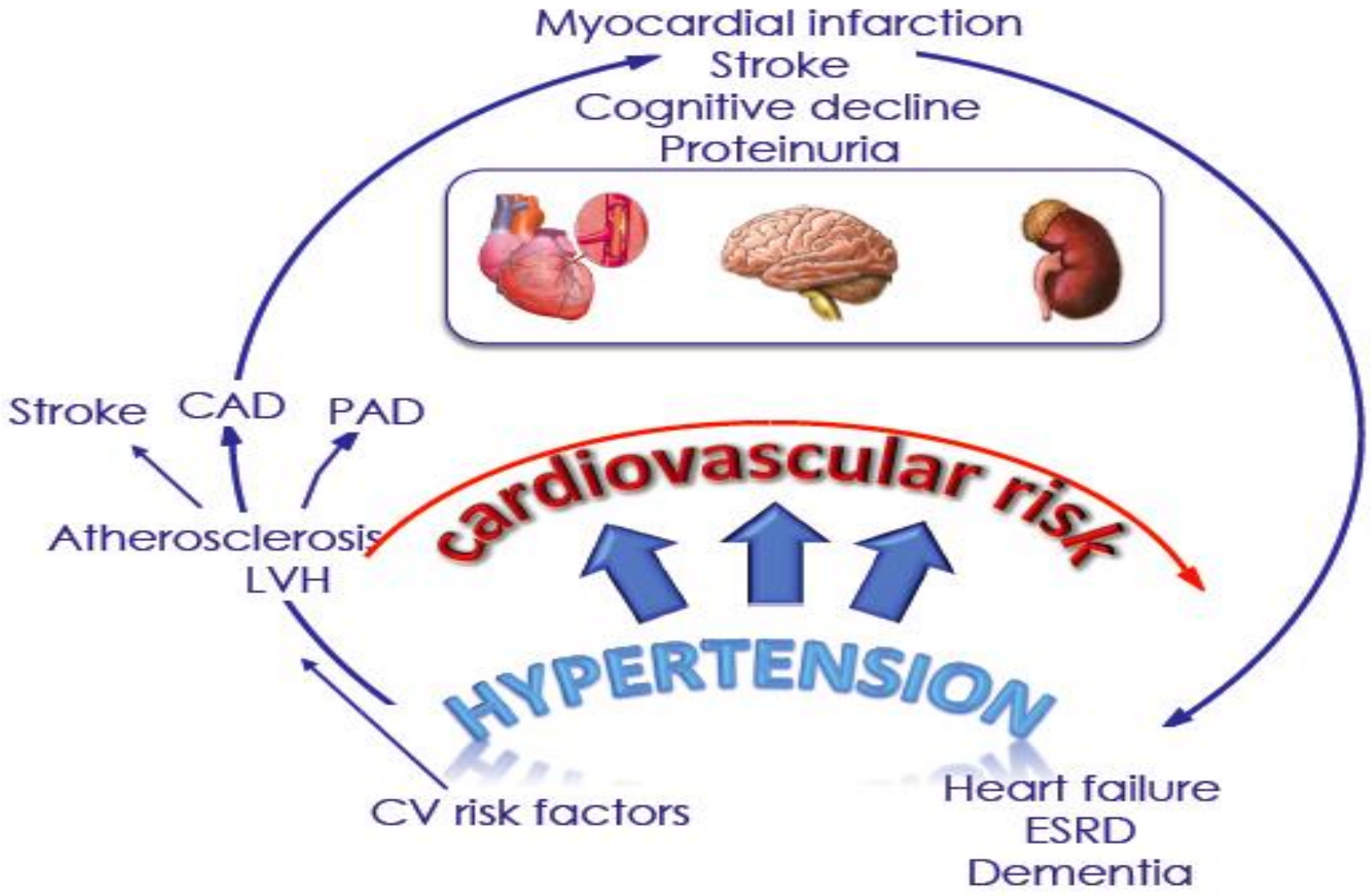
J Hypertens, 2013; 31: 1281-1357
Blood Pressure, 2013: 193-278

Ipertensione: una malattia in aumento

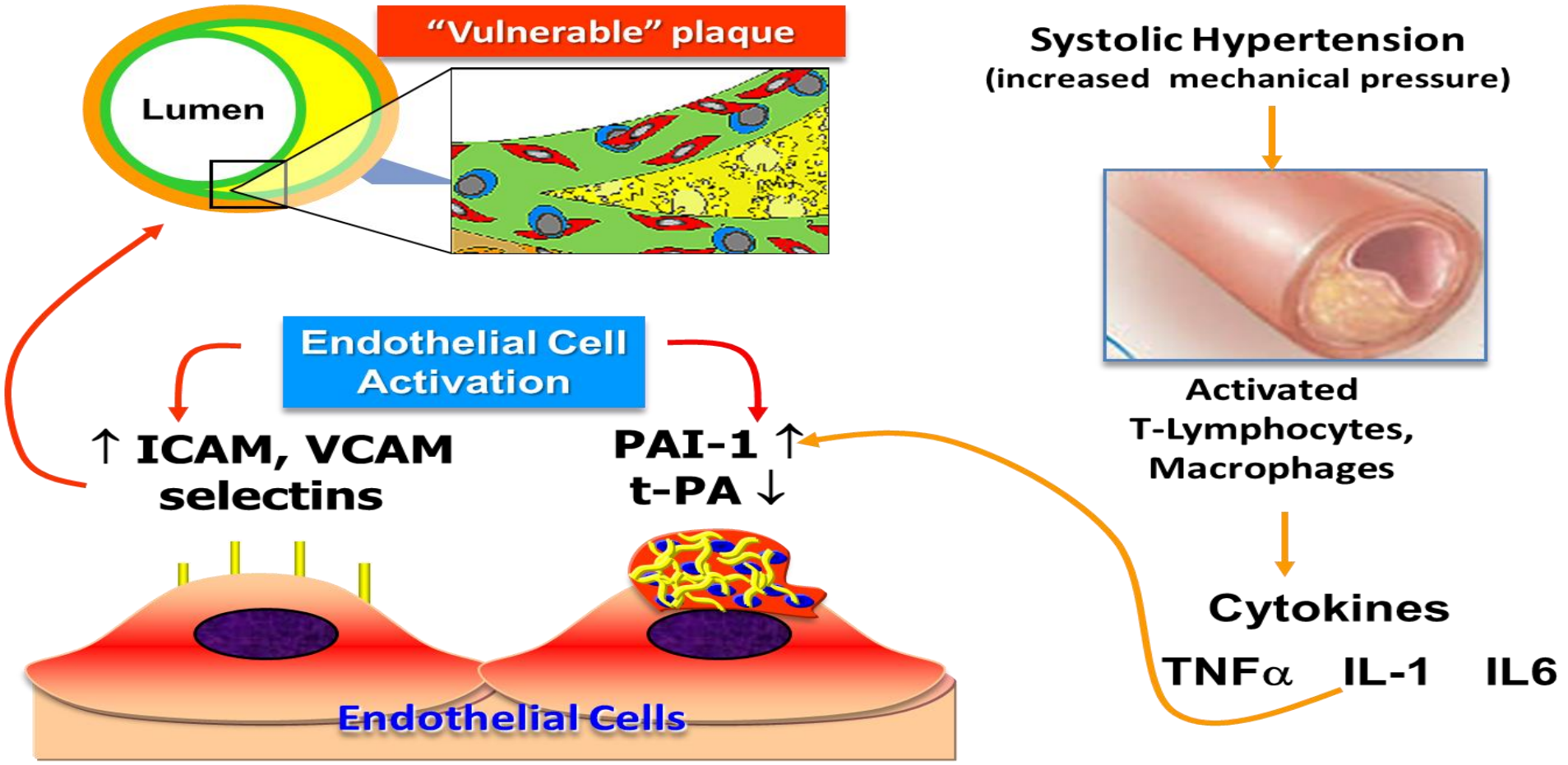


1.Rappresentazione grafica dei dati presenti nel testo da Kearney PM et al. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005;365:217-223.

L’ipertensione condiziona il continuum cardiovascolare

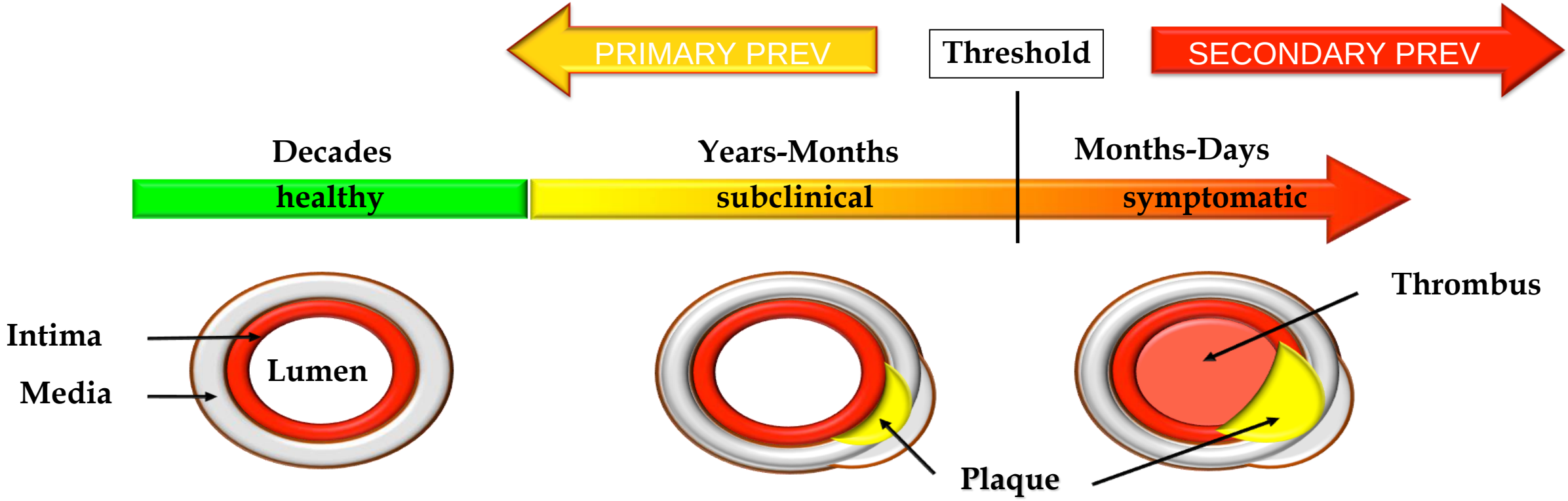


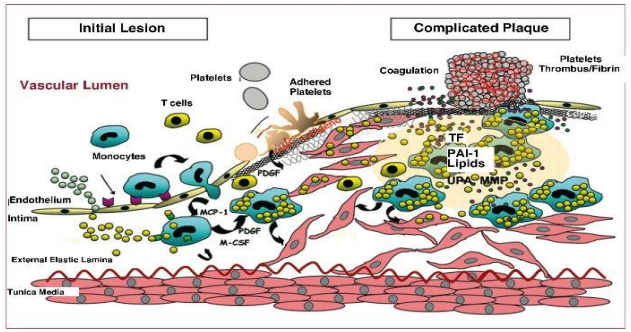
Increased pressure load as a stimulus to inflammation and vascular thrombosis



From Gabay C and Kushner I. N Engl J Med 1999. Libby P and Ridker PM. Circulation 1999; modified

Hypertension and atherosclerosis



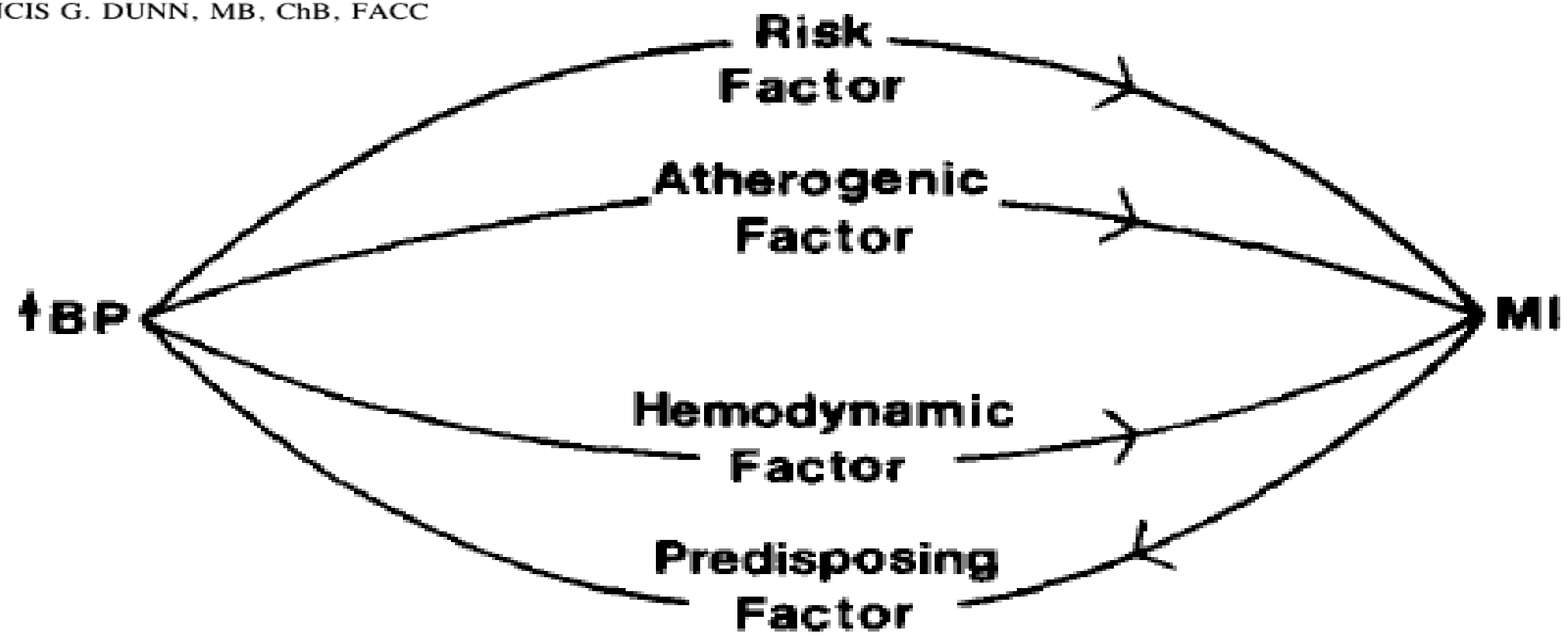


Ross R. N Eng J Med 199;340:115-126

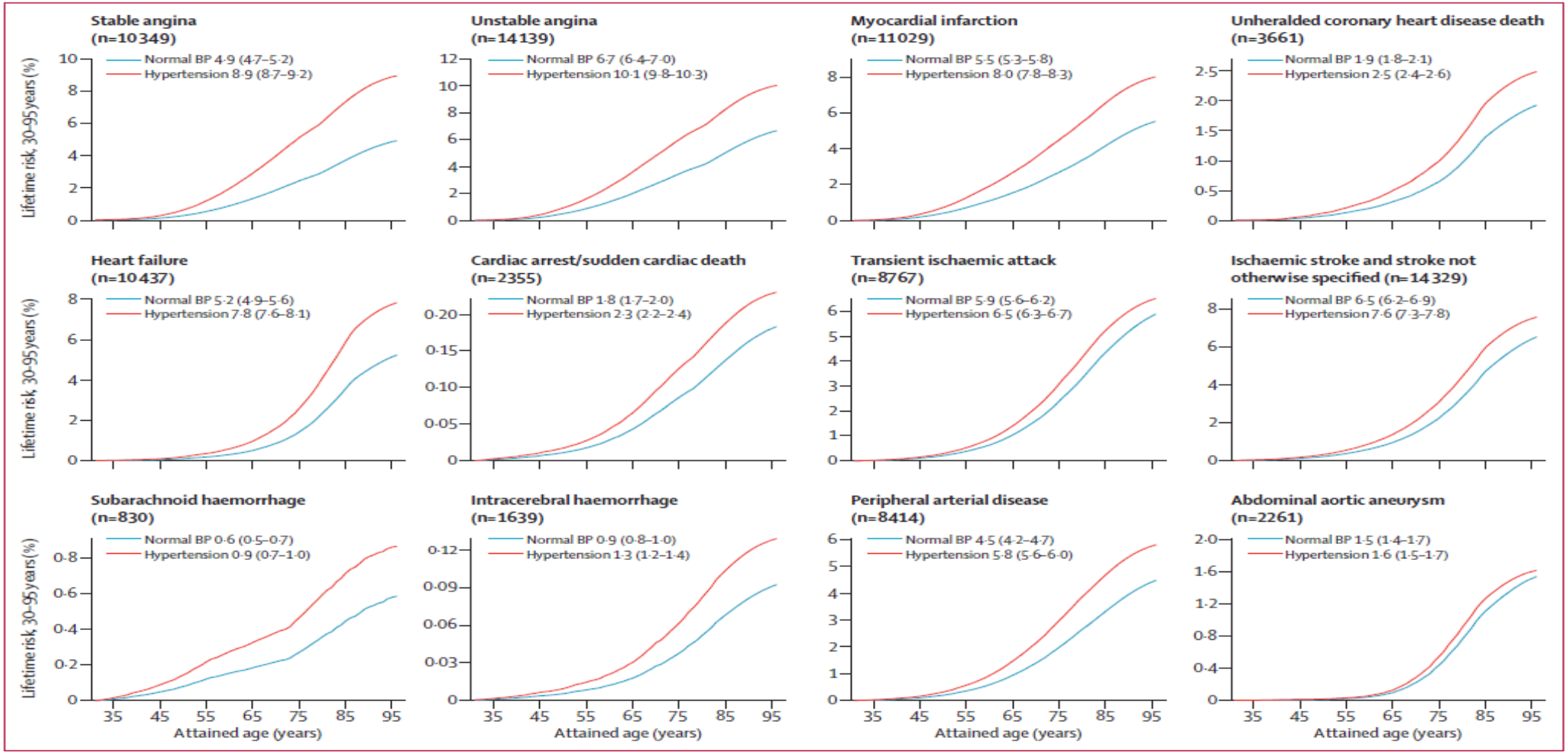
Hypertension and Myocardial Infarction

J AM COLL CARDIOL
1983;1(2):528–32

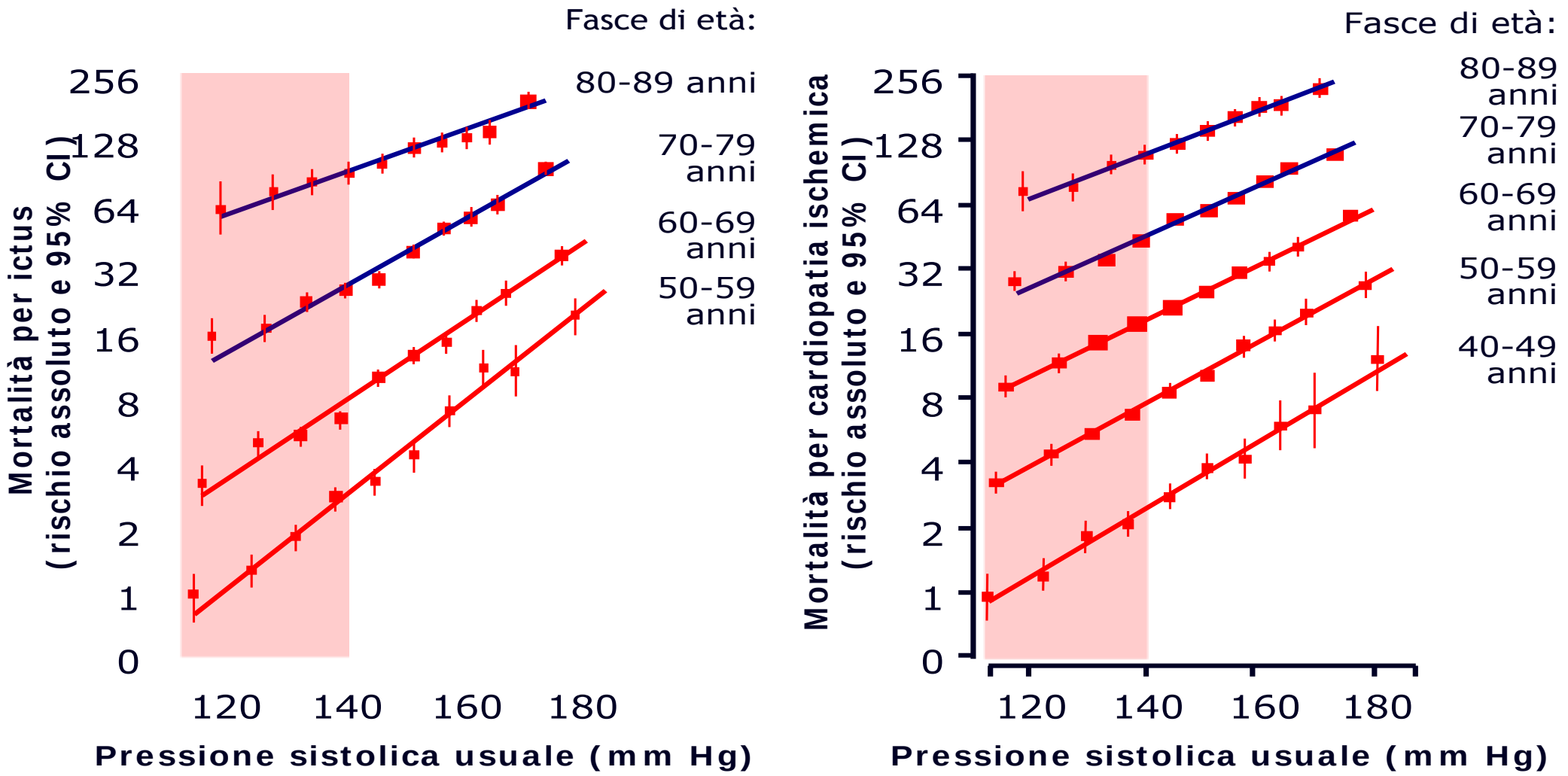
FRANCIS G. DUNN, MB, ChB, FACC



Lifetime risk (95% CI) of 12 different CVD in people with hypertension or normal BP from index age 30 years

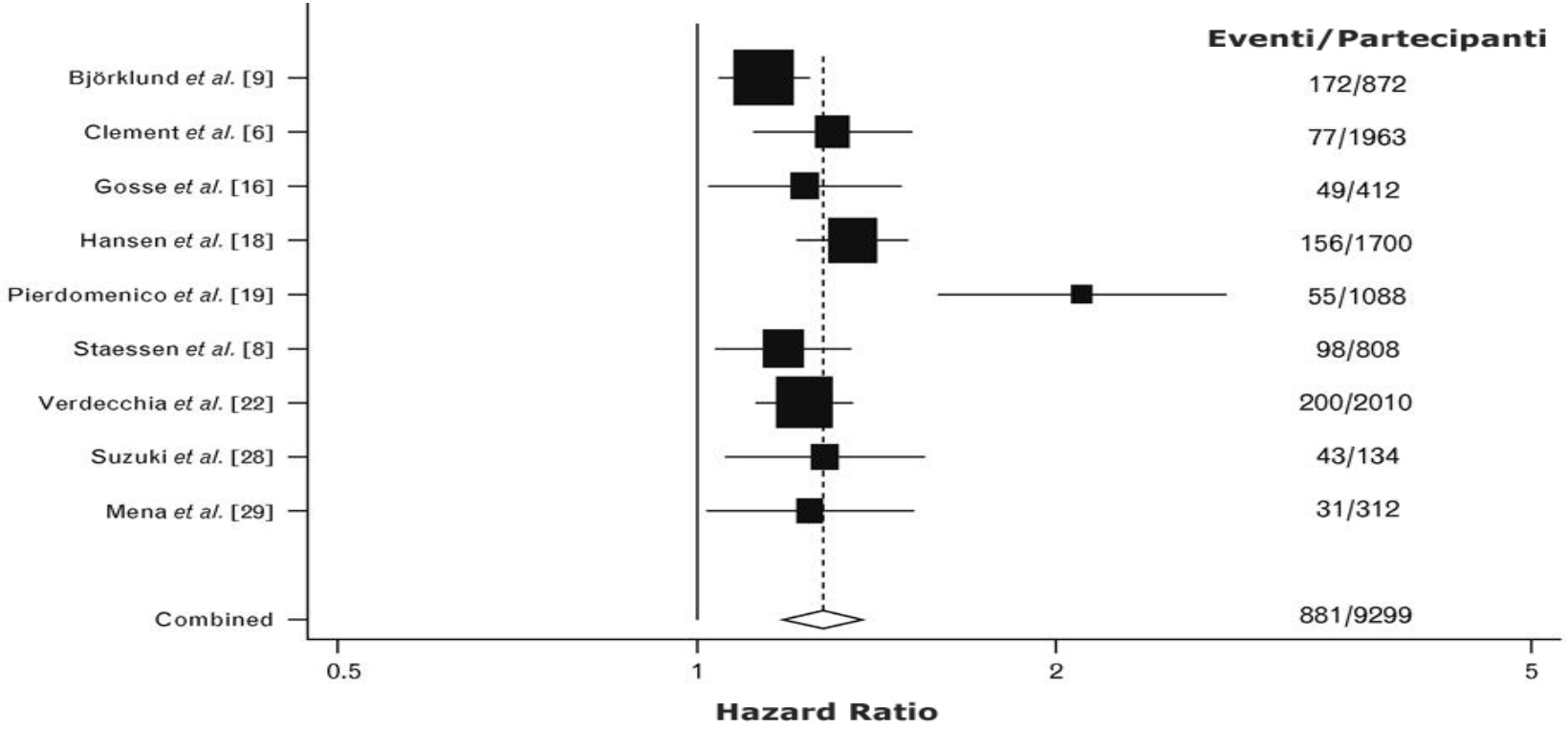


Rapsomaniki E et al. Lancet 2014; 383: 1899–911



Modificato da: Prospective Studies Collaboration. Lancet 2002;360:1903-1913

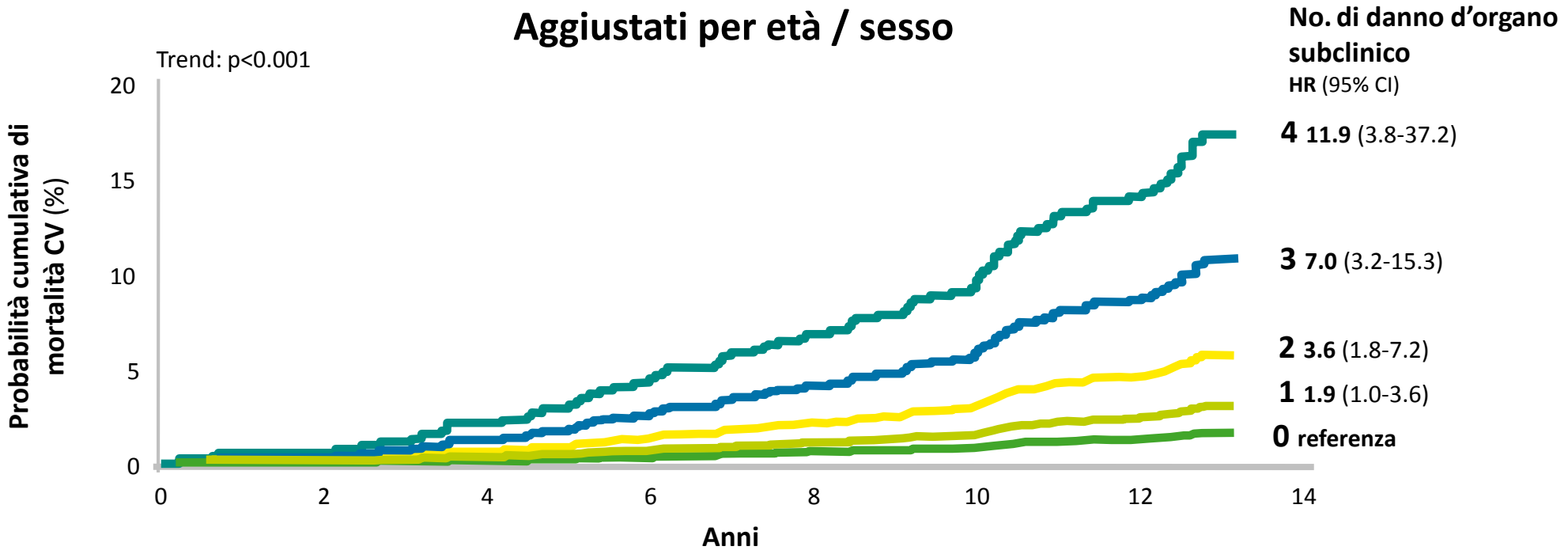
Metanalisi su 9 studi di coorte (n: 9299 pazienti) : La PAS nelle 24 h è un forte predittore di eventi cardiovascolari.



Esiste una FORTE ASSOCIAZIONE tra PAS nelle 24 h ed MACE:
Per ogni incremento di 10 mmHg di PAS media 24 h
→ + 1.33 vv Ictus
→ + 1.19 vv Mortalità CV
→ + 1.12 mortalità totale
→ → + 1.17 eventi cardiovascolari

Conen D and Bamberg F, J Hypertens 2008;26:1290

Probabilità cumulativa (%) e hazard ratio di mortalità CV in base al numero e tipo di danno d'organo subclinico *



No. di danno d'organo subclinico	0 (n=1127)	1 (n=563)	2 (n=206)	3 (n=60)	4 (n=12)
Hazard ratio (IC 95%) Aggiustati per età e sesso	1	1.9 (1.0–3.6)	3.6 (1.8–7.2)	7.0 (3.2–15.3)	11.9 (3.8–37.2)

* IVS / Placche aterosclerotiche / PWV >12 m/s / UACR ≥ 90° percentile

Sehestedt T, et al. Eur Heart J. 2010;31:883-91

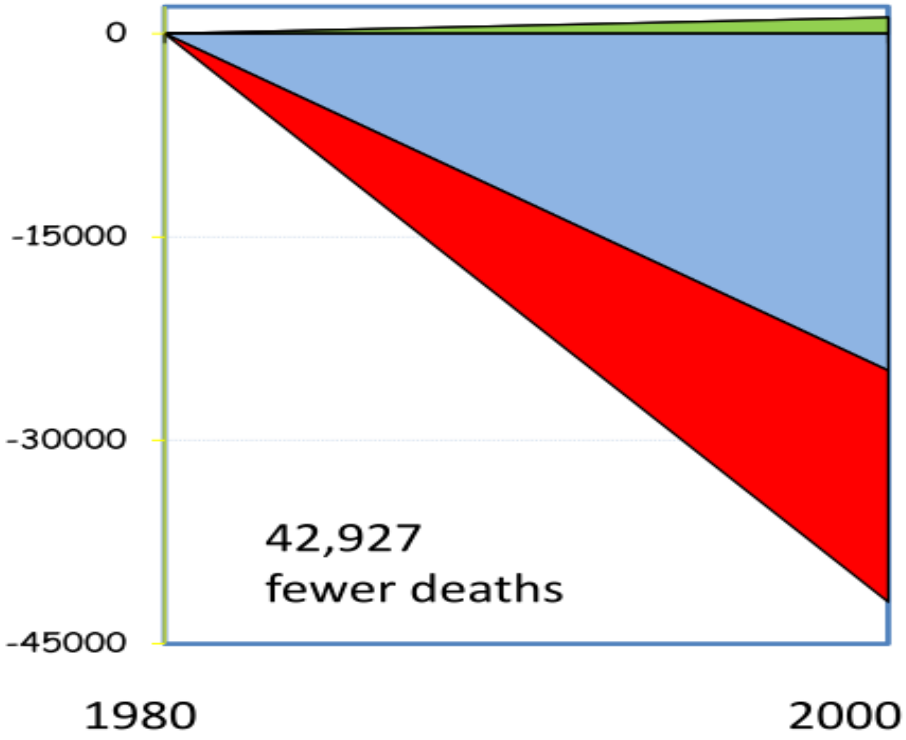
2013 ESH/ESC Guidelines for the management of arterial hypertension

European Heart Journal
doi:10.1093/eurheartj/eht151

Recommendations	Class [a]	Level [b]
Heart		
An ECG is recommended in all hypertensive patients to detect LVH, left atrial dilatation, arrhythmias, or concomitant heart disease.	I	B
In all patients with a history or physical examination suggestive of major arrhythmias, long-term ECG monitoring, and, in case of suspected exercise-induced arrhythmias, a stress ECG test should be considered.	IIa	C
An echocardiogram should be considered to refine CV risk, and confirm ECG diagnosis of LVH, left atrial dilatation or suspected concomitant heart disease, when these are suspected.	IIa	B
Whenever history suggests myocardial ischaemia, a stress ECG test is recommended, and, if positive or ambiguous, an imaging stress test (stress echocardiography, stress cardiac magnetic resonance or nuclear scintigraphy) is recommended.	I	C
Arteries		
Ultrasound scanning of carotid arteries should be considered to detect vascular hypertrophy or asymptomatic atherosclerosis, particularly in the elderly.	IIa	B
Carotid–femoral PWV should be considered to detect large artery stiffening.	IIa	B
Ankle–brachial index should be considered to detect PAD.	IIa	B

How much is important to treat risk factors in secondary prevention?

Explaining the fall in coronary heart disease deaths in Italy 1980-2000



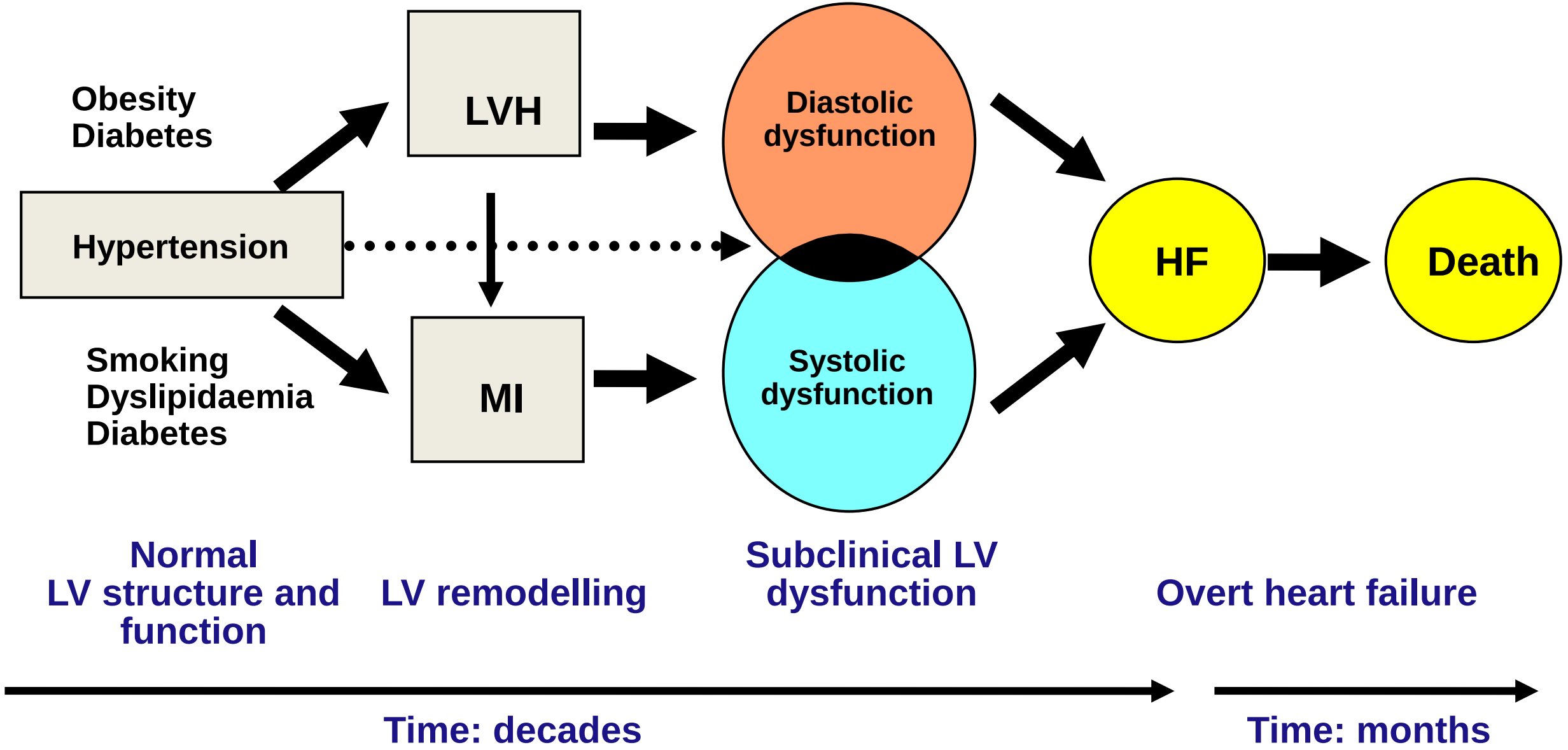
Risk Factors worse	*+3 %*	
Obesity (increase)		+ 0.6 %
Diabetes (increase)		+ 2.2 %
Risk Factors better	*–58 %*	
Smoking		- 3.7 %
Cholesterol		-23.4 %
Population BP fall		-25.0 %
Physical activity (incr.)	- 5.8 %	
Treatments	*-40 %*	
AMI treatments		- 4.9 %
Secondary prevention		- 6.1 %
Heart failure		-13.7 %
Community Angina		- 8.7 %
CABG & PTCA		- 1.1 %
Unst.Angina: Aspirin etc		- 1.0 %
Hypertension therapies		- 1.5 %
Statins 1° prevention		- 2.7 %

Palmieri L et al. Am J Public Health. 2010; 100:684–692

The Major Risk Factors for the Development of Heart Failure

- Hypertension
- Myocardial infarction
- Angina pectoris
- Diabetes
- Left ventricular hypertrophy
- Valvular disease

Progression from Hypertension to Heart Failure

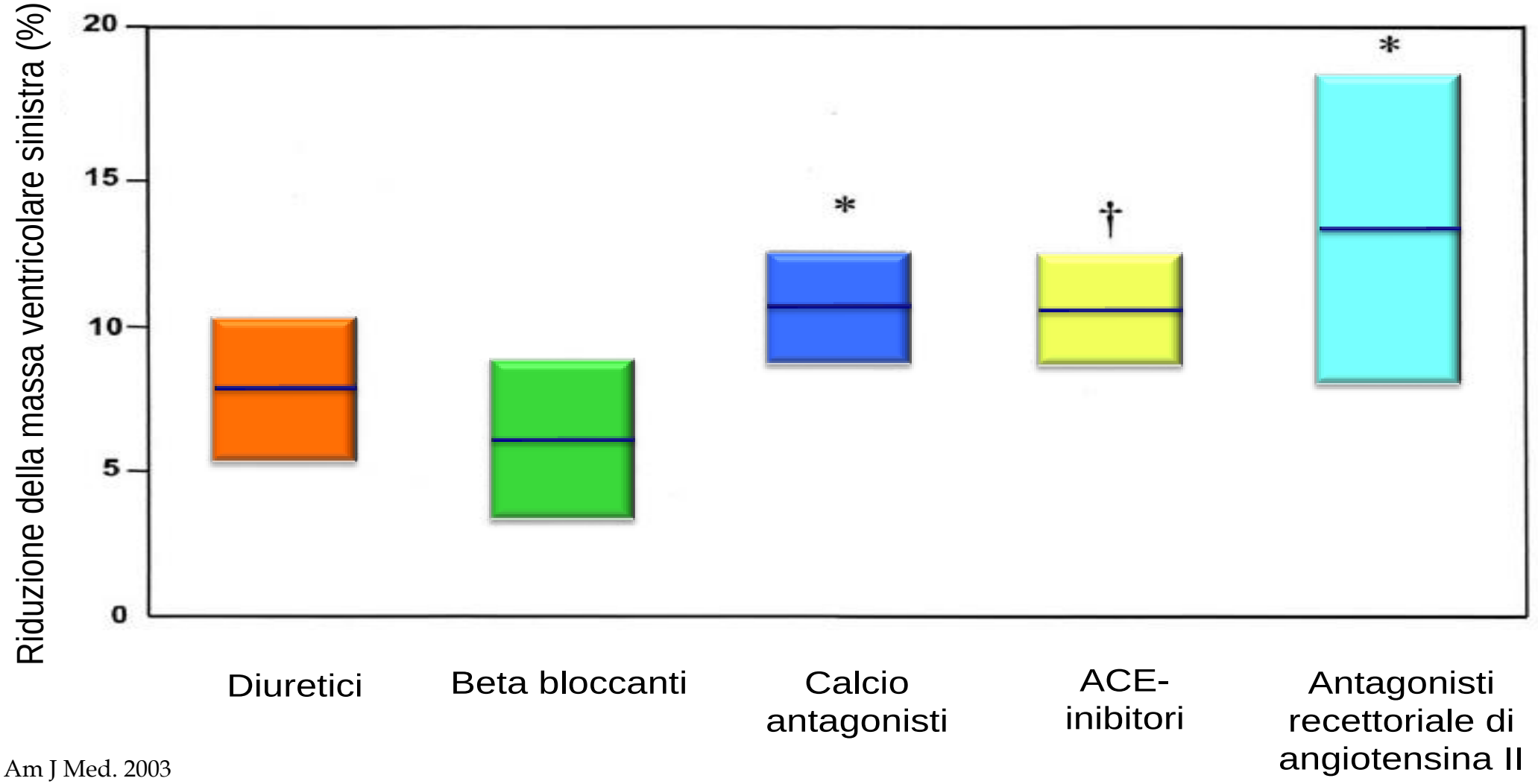


Trattamento dell'ipertensione ed eventi cardiovascolari

- ↓38% del rischio di ictus
- ↓16% del rischio di cardiopatia coronarica
- ↓21% di mortalità cardiovascolare
- ↓35% dell'incidenza di ipertrofia ventricolare Sx
- ↓52% dell'incidenza di insufficienza cardiaca congestizia

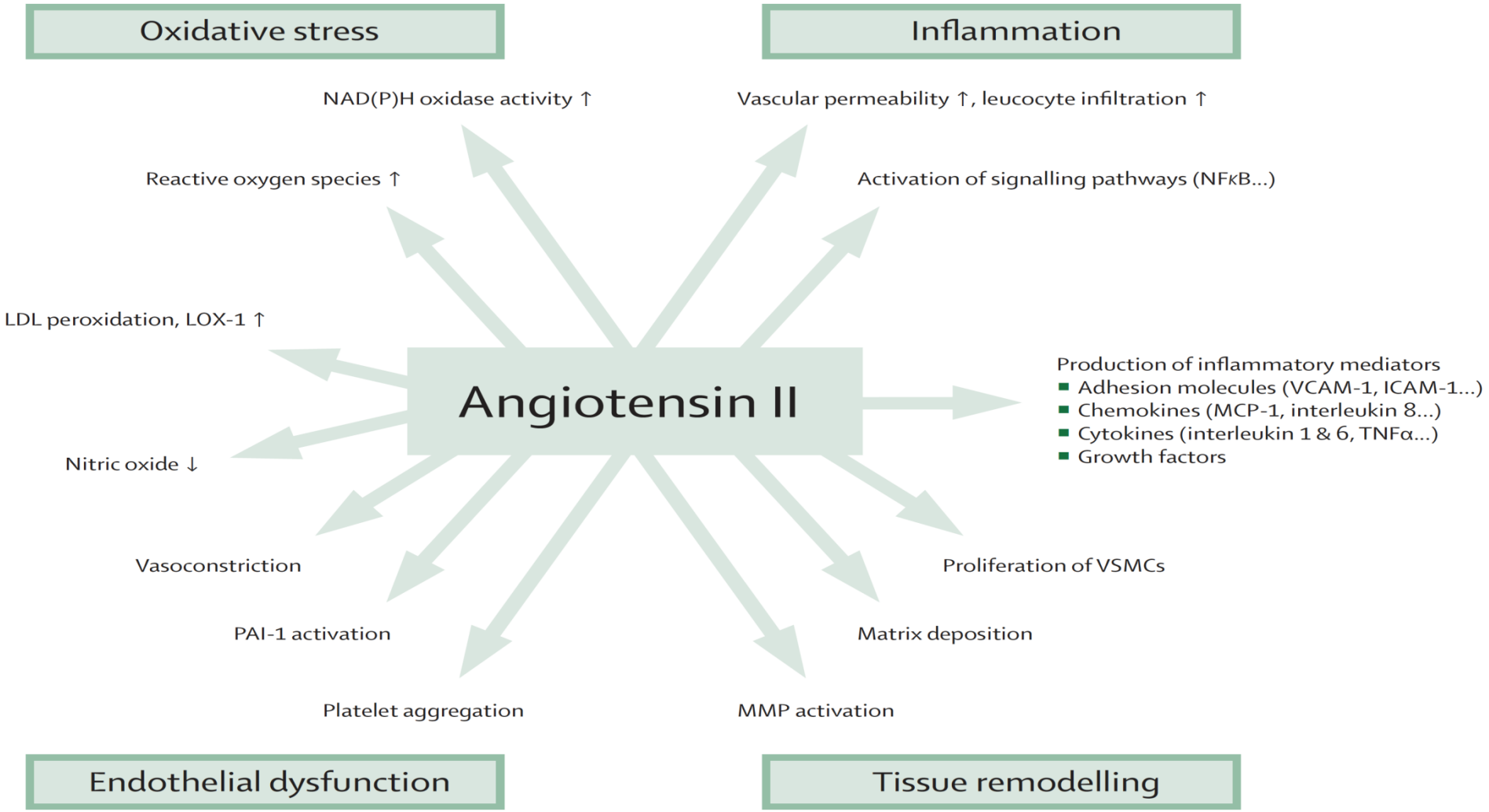
BHS Guidelines J Human Hypert 2000; 13: 569-75 - JACC 1996; 27: 1214-9

Effetti della terapia antipertensiva sulla regressione della ipertrofia ventricolare sinistra



Klingbeil et al, Am J Med. 2003

Renin-angiotensin system and CV risk



Schmieder et al. Lancet 2007;369:1208–1219

2013 ESH/ESC Guidelines for the management of arterial hypertension

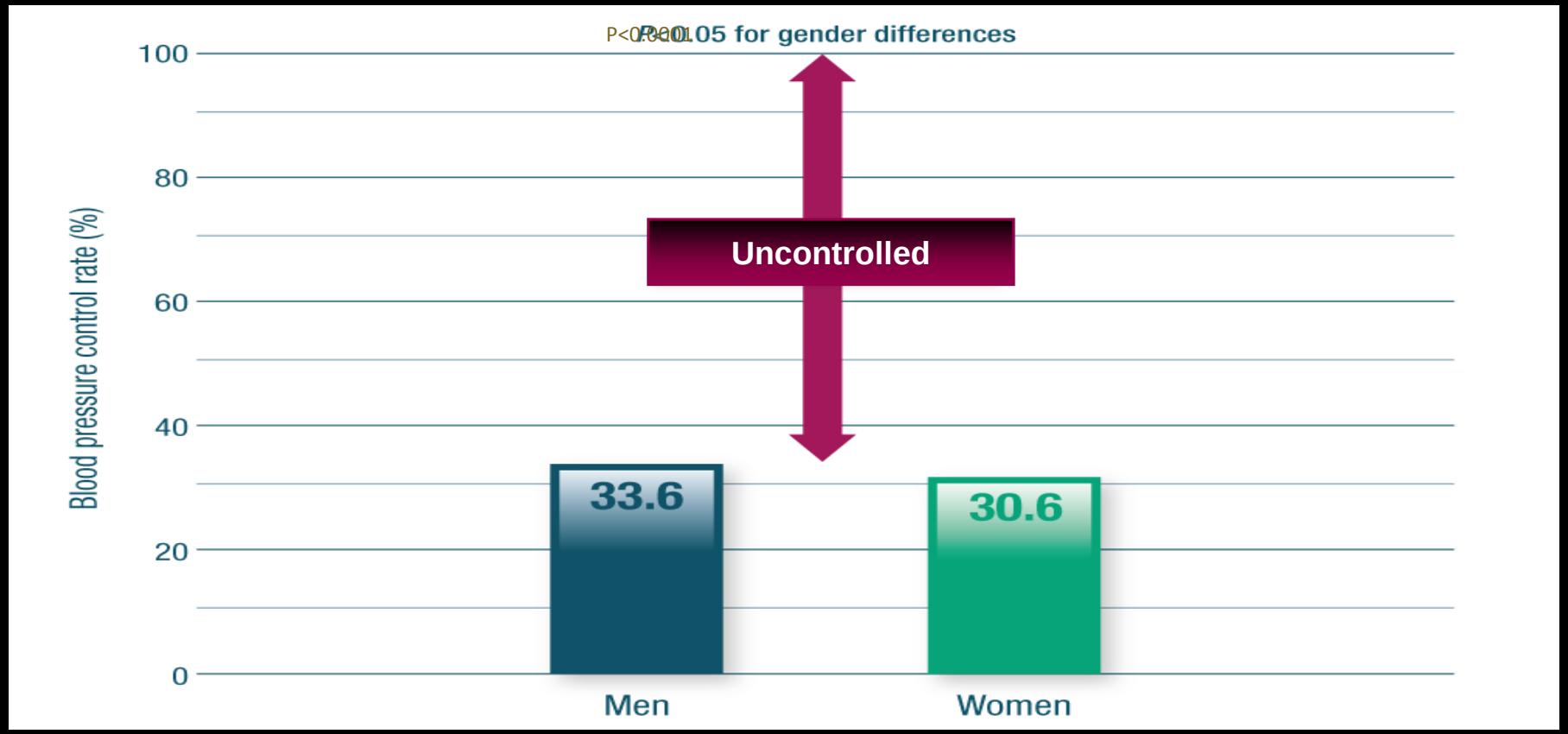
Condition	Drug
Asymptomatic organ damage	
LVH	ACE inhibitor, calcium antagonist, ARB
Asymptomatic atherosclerosis	Calcium antagonist, ACE inhibitor
Microalbuminuria	ACE inhibitor, ARB
Renal dysfunction	ACE inhibitor, ARB
Clinical CV event	
Previous stroke	Any agent effectively lowering BP
Previous myocardial infarction	BB, ACE inhibitor, ARB
Angina pectoris	BB, calcium antagonist
Heart failure	Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonists
Aortic aneurysm	BB
Atrial fibrillation, prevention	Consider ARB, ACE inhibitor, BB or mineralocorticoid receptor antagonist
Atrial fibrillation, ventricular rate control	BB, non-dihydropyridine calcium antagonist
ESRD/proteinuria	ACE inhibitor, ARB
Peripheral artery disease	ACE inhibitor, calcium antagonist
Other	
ISH (elderly)	Diuretic, calcium antagonist
Metabolic syndrome	ACE inhibitor, ARB, calcium antagonist
Diabetes mellitus	ACE inhibitor, ARB
Pregnancy	Methyldopa, BB, calcium antagonist
Blacks	Diuretic, calcium antagonist

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BB = beta-blocker; BP = blood pressure; CV = cardiovascular; ESRD = end-stage renal disease; ISH = isolated systolic hypertension; LVH = left ventricular hypertrophy.

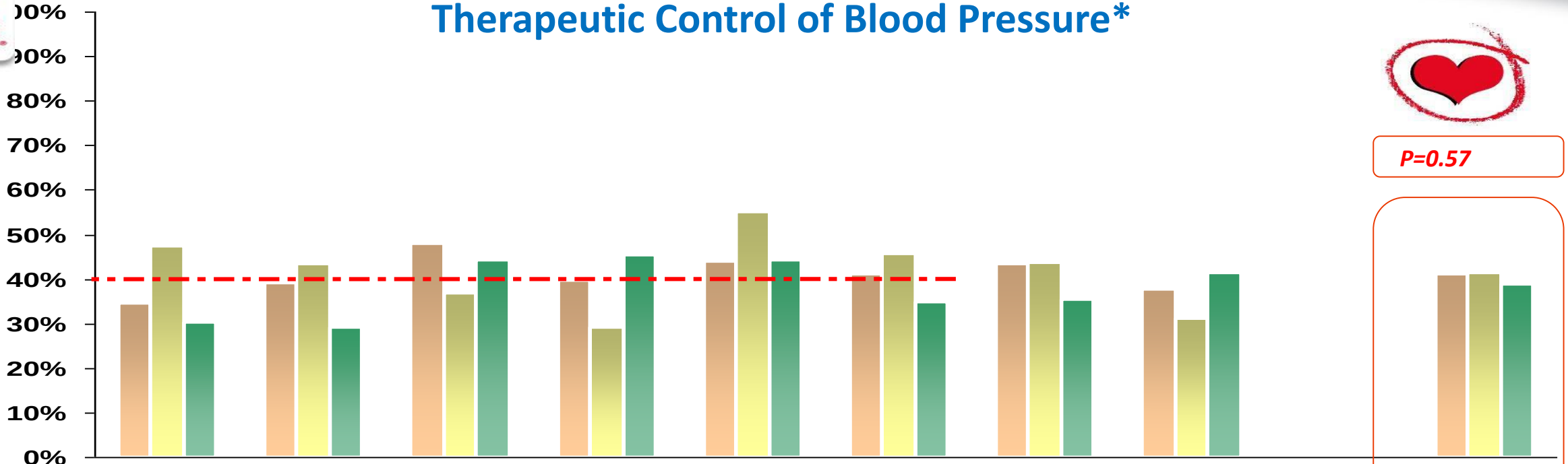
Il controllo della pressione arteriosa è insoddisfacente

- Il tasso di controllo della pressione arteriosa sistolica e diastolica è stato raggiunto nel 33.6% degli uomini e nel 30.6% delle donne sul totale della popolazione

1



Therapeutic Control of Blood Pressure*



	Czech Rep.	Finland	France	Germany	Hungary	Italy	Netherlands	Slovenia	ALL
Survey 1	34,4%	39,1%	47,9%	39,7%	44,0%	41,0%	43,3%	37,7%	41,0%
Survey 2	47,2%	43,4%	36,7%	29,1%	55,0%	45,7%	43,5%	31,1%	41,2%
Survey 3	30,1%	29,1%	44,1%	45,2%	44,1%	34,8%	35,3%	41,4%	38,7%

* SBP/DBP < 140/90 mmHg for non-diabetics or < 130/80 mmHg for diabetics

European Heart Journal
doi:10.1093/eurheartj/eht151

2013 ESH/ESC guidelines for the management of arterial hypertension

ESH/ESC Joint Task Force

Chairmen: Giuseppe Mancia (Italy), Robert Fagard (Belgium)

1.2 New aspects

(1) Epiden…tension and BP control in Europe.
(2) Streng… pressure monit… ment of hyp… itoring (ABPM).
(3) Update of the prognostic significance of night-time BP, white coat hypertension and masked hypertension.
(4) Re-emphasis on integration of BP, cardiovascular (CV) risk factors, asymptomatic organ damage (OD) and clinical complications for total CV risk assessment.
(5) Update of the prognostic significance of asymptomatic OD, including heart, blood vessels, kidney, eye and brain.
(6) Reconsideration of the risk of overweight and target body mass index (BMI) in hypertension.
(7) Hypertension in young people.
(8) Initiation of antihypertensive treatment. More evidence-based criteria and no drug treatment of high normal BP.
(9) Target BP for treatment. More evidence-based criteria and unified target systolic blood pressure (SBP) (<140 mmHg) in both higher and lower CV risk patients.
… to initial monotherapy, without any all-ranking
(13) Extended section … conditions.
(14) Revised recommendations on treatment of hyp… in the elderly.
(15) Drug treatment of octogenarians.
(16) Special attention to resistant hypertension and new treatment approaches.
(17) Increased attention to OD-guided therapy.
(18) New approaches to chronic management of hypertensive disease.

(9) Target BP was changed. A unified target systolic blood pressure (SBP) (<140 mmHg) was given in both higher and lower CV risk patients.

BP target

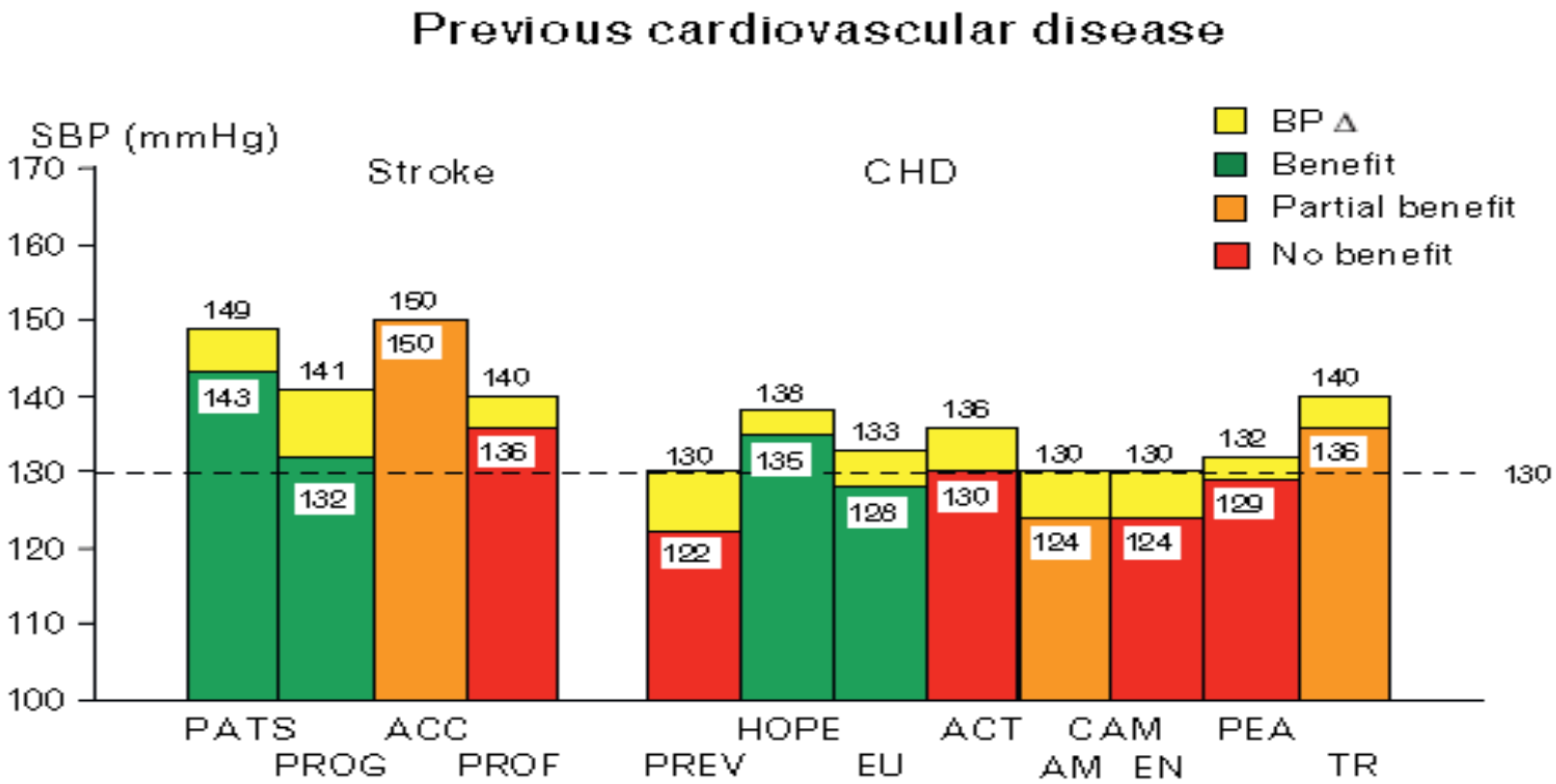
A unified target systolic blood pressure (<140 mmHg) was given in both higher and lower CV risk patients

Blood pressure goals in hypertensive patients

Recommendations	Class [a]	Level [b]	Ref. [c]
A SBP goal <140 mmHg:			
a) is recommended in patients at low–moderate CV risk;	I	B	266, 269, 270
b) is recommended in patients with diabetes;	I	A	270, 275, 276
c) should be considered in patients with previous stroke or TIA;	IIa	B	296, 297
d) should be considered in patients with CHD;	IIa	B	141, 265
e) should be considered in patients with diabetic or non-diabetic CKD.	IIa	B	312, 313
In elderly hypertensives less than 80 years old with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg.	I	A	265
In fit elderly patients less than 80 years old SBP values <140 mmHg may be considered, whereas in the fragile elderly population SBP goals should be adapted to individual tolerability.	IIb	C	-
In individuals older than 80 years and with initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg provided they are in good physical and mental conditions.	I	B	287
A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated.	I	A	269, 290, 293

CHD — coronary heart disease; CKD — chronic kidney disease; CV — cardiovascular; DBP — diastolic blood pressure; SBP — systolic blood pressure; TIA — transient ischaemic attack.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

Threshold/Target BP goals



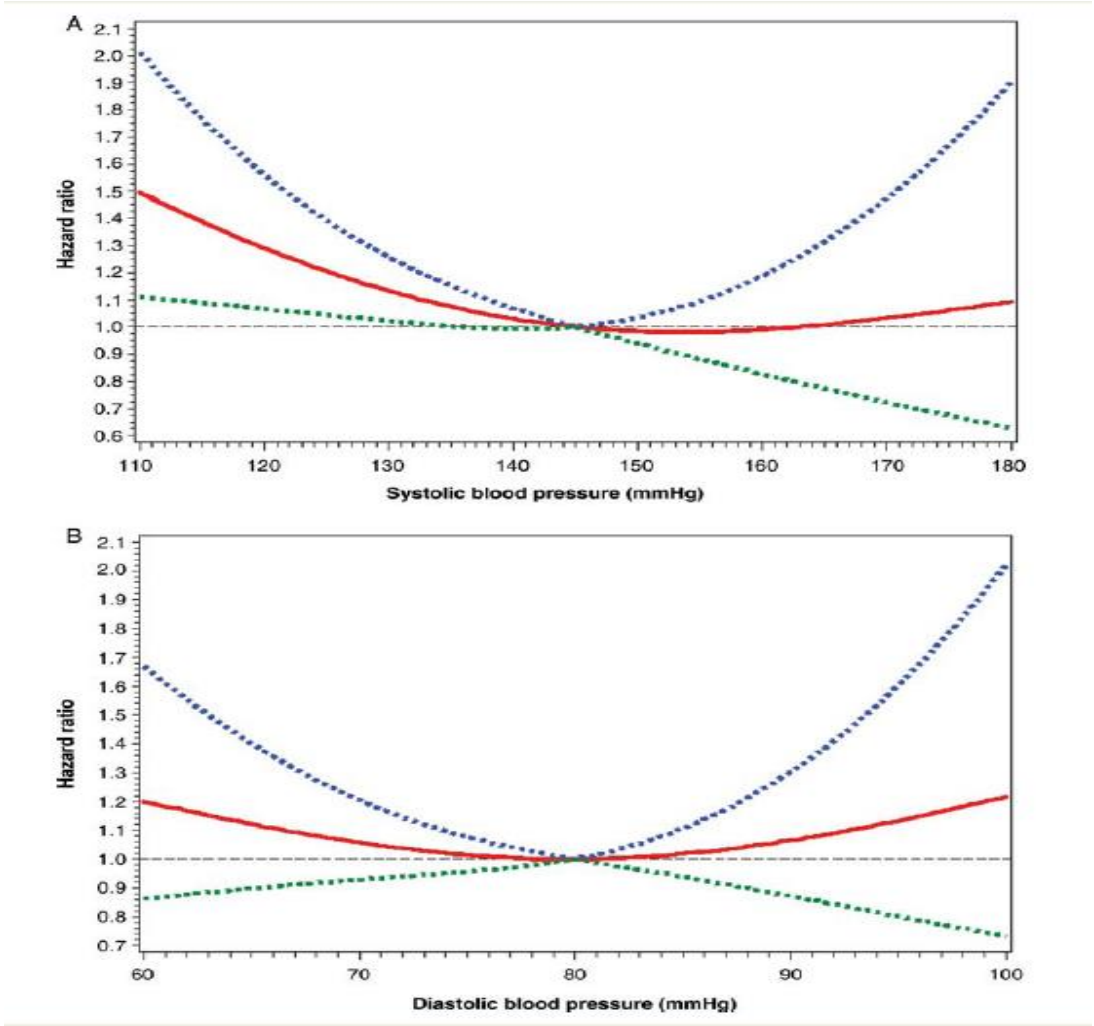
Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document

ESH 2009 guidelines reappraisal

Lower is not always better: L'effetto J

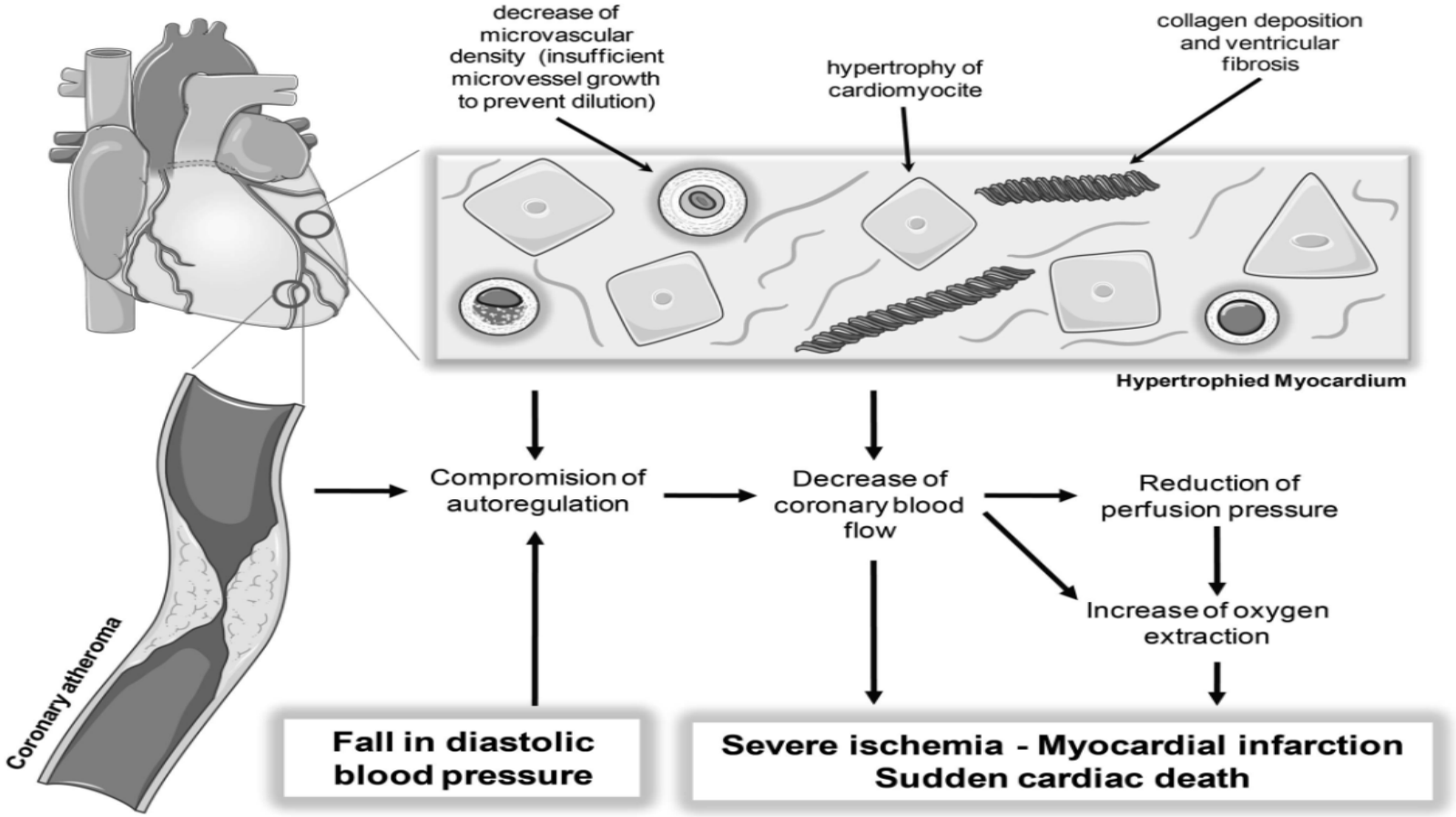
Nella popolazione generale vale la proporzionalità diretta tra riduzione dei valori pressori e riduzione di eventi cardiovascolari, ma NEI PAZIENTI CON MALATTIE CARDIOVASCOLARI (soprattutto quelli con CAD), la relazione tra BP e outcomes cardiovascolari segue una distribuzione bimodale :

a VALORI ESTREMI il rischio cardiovascolare e il rischio di morte per tutte le cause AUMENTA



European Heart Journal (2010) 31, 2897–2908

Threshold/Target BP goals?



Lower is not always better: Spiegazioni per l'effetto J

1)La riduzione dei valori pressori può essere un epifenomeno di altre condizioni cliniche debilitanti come cancro che comportano di per sé un aumento della mortalità complessiva e per cause cardiovascolari

2) La riduzione dei valori pressori può essere la conseguenza di malattie cardiache che determinano bassa portata

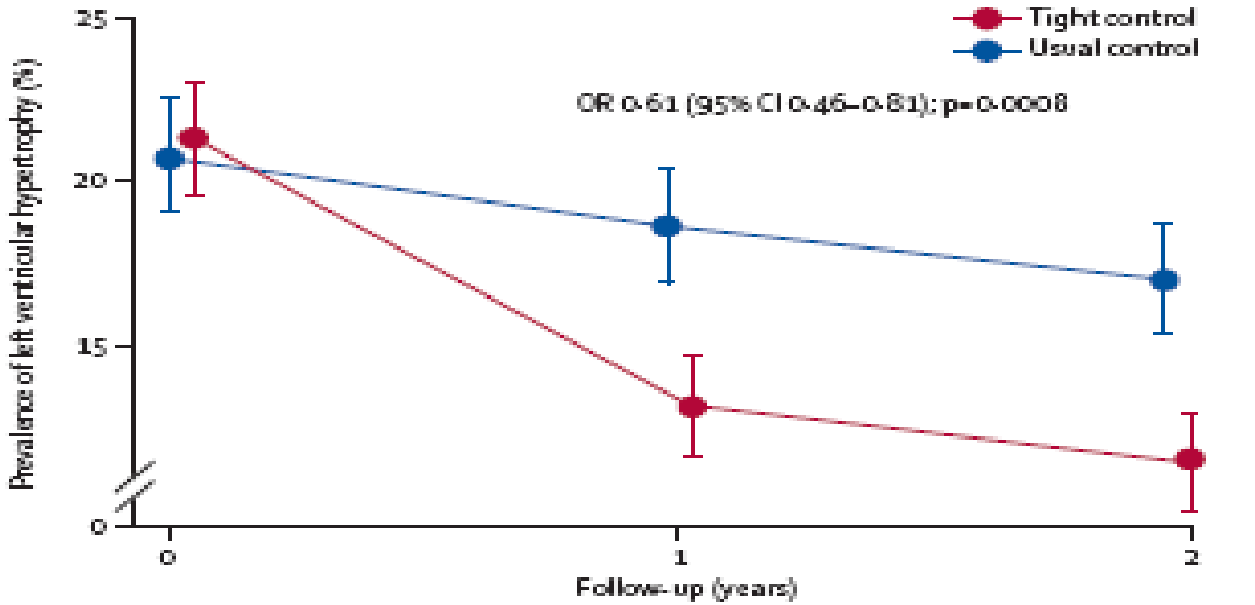
3) La riduzione dei valori pressori può essere lo specchio del danno vascolare espresso nella "vascular stifness"

4)L'abbassamento dei valori di PA (soprattutto diastolica), riduce il flusso coronarico

European Heart Journal (2010) 31, 2897–2908

Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial

*Paolo Verdecchia, Jan A Staessen, Fabio Angeli, Giovanni de Simone, Augusto Achilli, Antonello Ganau, Gianfrancesco Mureddu, Sergio Pede, Aldo P Maggioni, Donata Lucci, Gianpaolo Reboldi, on behalf of the Cardio-Sis investigators**



Number of events/ number of patients			
Usual control	114/548	92/493	82/483
Tight control	118/553	64/487	55/484

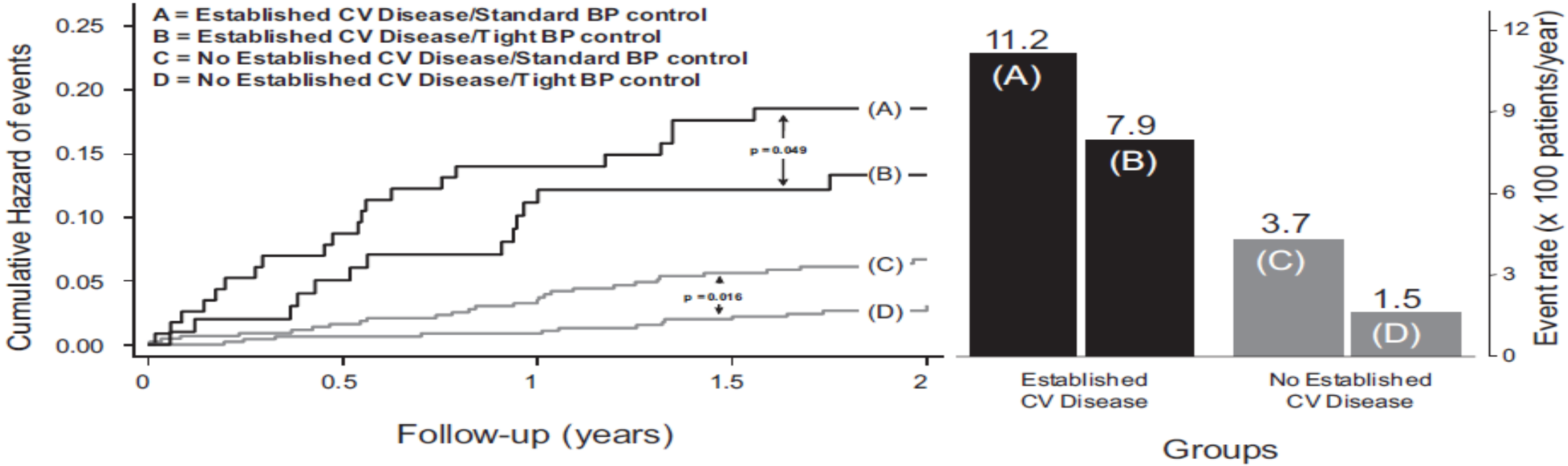
- **Tight <130 mmHg**
- **Usual <140 mmHg**

Drugs	
Diuretics	259 (47%)
β blockers	212 (38%)
ACE inhibitors	243 (44%)
Angiotensin-receptor blockers	159 (29%)
Calcium-channel blockers	196 (35%)
α1 blockers	52 (9%)
Centrally acting drugs	13 (2%)
Statins	128 (23%)
Aspirin	104 (19%)

Lancet 2009; 374: 525–33

Tight Versus Standard Blood Pressure Control in Patients With Hypertension With and Without Cardiovascular Disease

absence (n=895) or presence (n=216) of established cardiovascular disease at entry



the Cardio-Sis Investigators

Hypertension. 2014;63:475-482

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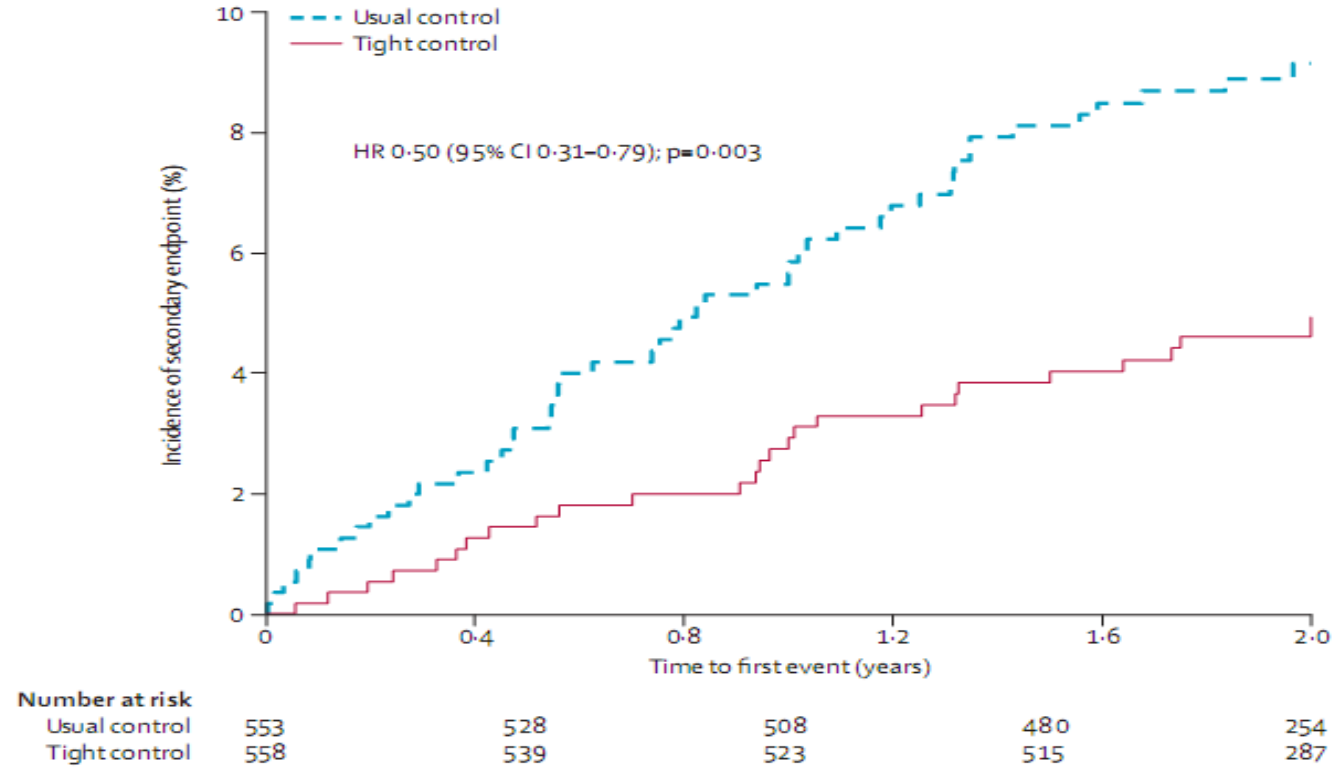
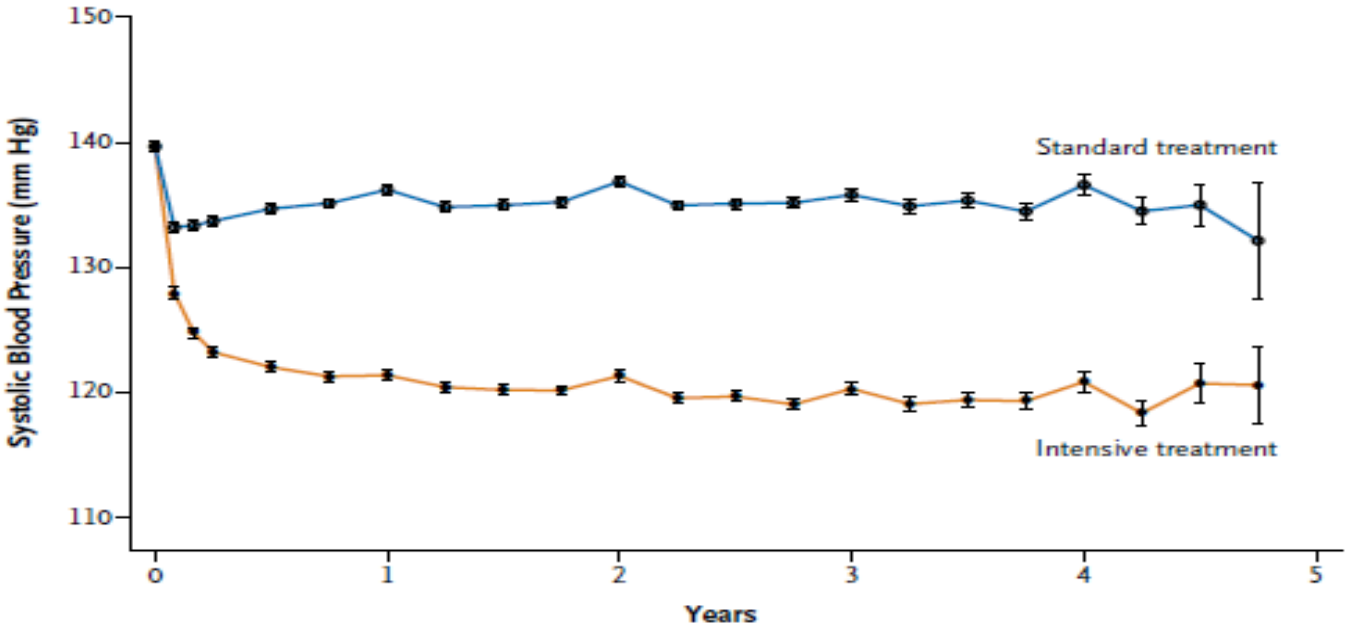


- **Tight <130 mmHg**
- **Usual <140 mmHg**

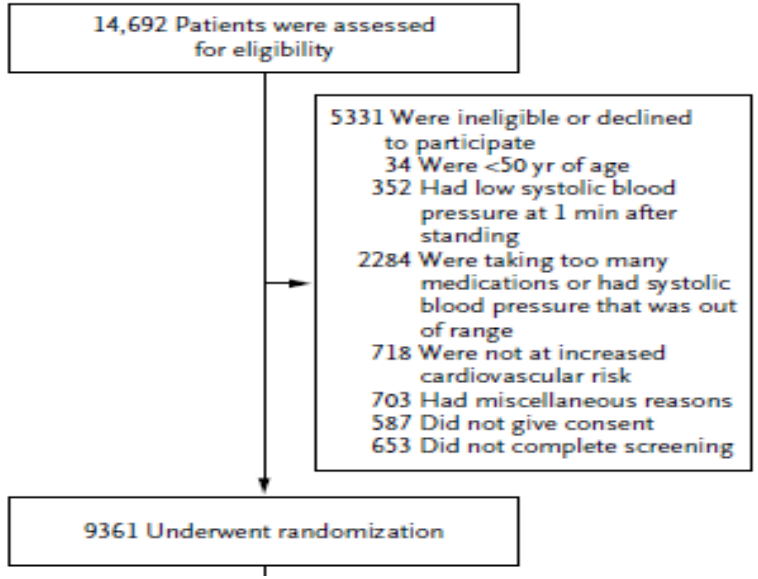
Lancet 2009; 374: 525–33

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*



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



121.5 mm Hg vs. 134.6 mm Hg

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2015;373:2103-16.

A Randomized Trial of Intensive versus Standard Blood-Pressure Control
The SPRINT Research Group*

BP target <130/80 mm Hg

Table 2. Primary and Secondary Outcomes and Renal Outcomes.*

Outcome	Intensive Treatment		Standard Treatment		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*% per year*	*no. of patients (%)*	*% per year*		
All participants	**(N=4678)**		**(N=4683)**			
Primary outcome†	243 (5.2)	1.65	319 (6.8)	2.19	0.75 (0.64–0.89)	<0.001
Secondary outcomes						
Myocardial infarction	97 (2.1)	0.65	116 (2.5)	0.78	0.83 (0.64–1.09)	0.19
Acute coronary syndrome	40 (0.9)	0.27	40 (0.9)	0.27	1.00 (0.64–1.55)	0.99
Stroke	62 (1.3)	0.41	70 (1.5)	0.47	0.89 (0.63–1.25)	0.50
Heart failure	62 (1.3)	0.41	100 (2.1)	0.67	0.62 (0.45–0.84)	0.002
Death from cardiovascular causes	37 (0.8)	0.25	65 (1.4)	0.43	0.57 (0.38–0.85)	0.005
Death from any cause	155 (3.3)	1.03	210 (4.5)	1.40	0.73 (0.60–0.90)	0.003
Primary outcome or death	332 (7.1)	2.25	423 (9.0)	2.90	0.78 (0.67–0.90)	<0.001
Participants with CKD at baseline	**(N=1330)**		**(N=1316)**			
Composite renal outcome‡	14 (1.1)	0.33	15 (1.1)	0.36	0.89 (0.42–1.87)	0.76
≥50% reduction in estimated GFR§	10 (0.8)	0.23	11 (0.8)	0.26	0.87 (0.36–2.07)	0.75
Long-term dialysis	6 (0.5)	0.14	10 (0.8)	0.24	0.57 (0.19–1.54)	0.27
Kidney transplantation	0		0			
Incident albuminuria¶	49/526 (9.3)	3.02	59/500 (11.8)	3.90	0.72 (0.48–1.07)	0.11
Participants without CKD at baseline‖	**(N=3332)**		**(N=3345)**			
≥30% reduction in estimated GFR to <60 ml/min/1.73 m^2§	127 (3.8)	1.21	37 (1.1)	0.35	3.49 (2.44–5.10)	<0.001
Incident albuminuria¶	110/1769 (6.2)	2.00	135/1831 (7.4)	2.41	0.81 (0.63–1.04)	0.10

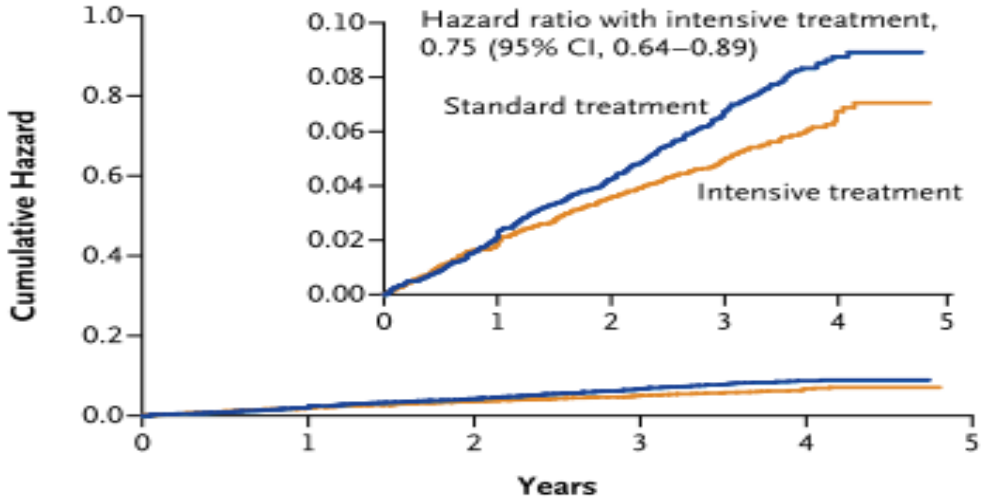
N Engl J Med 2015;373:2103-16.

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

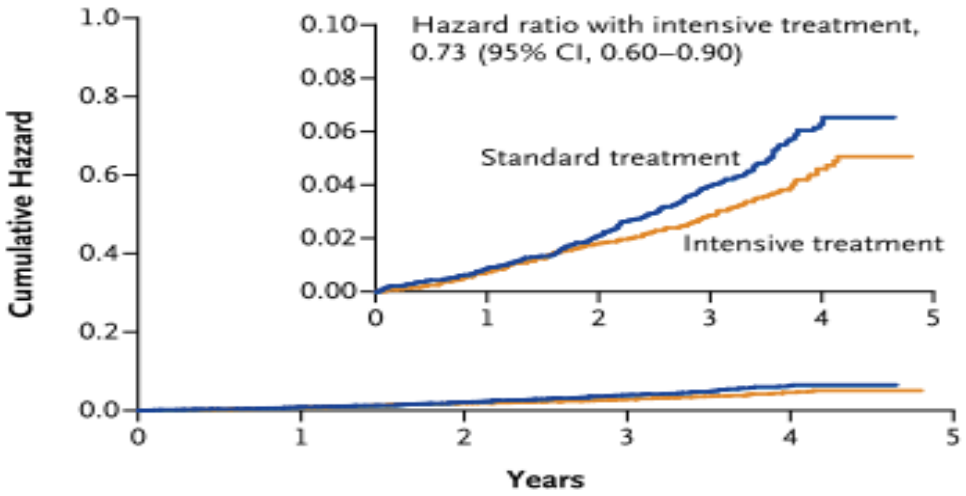
BP target <130/80 mm Hg

A Primary Outcome



No. at Risk					
Standard treatment	4683	4437	4228	2829	721
Intensive treatment	4678	4436	4256	2900	779

B Death from Any Cause



No. at Risk					
Standard treatment	4683	4528	4383	2998	789
Intensive treatment	4678	4516	4390	3016	807

The NEW ENGLAND JOURNAL of MEDICINE

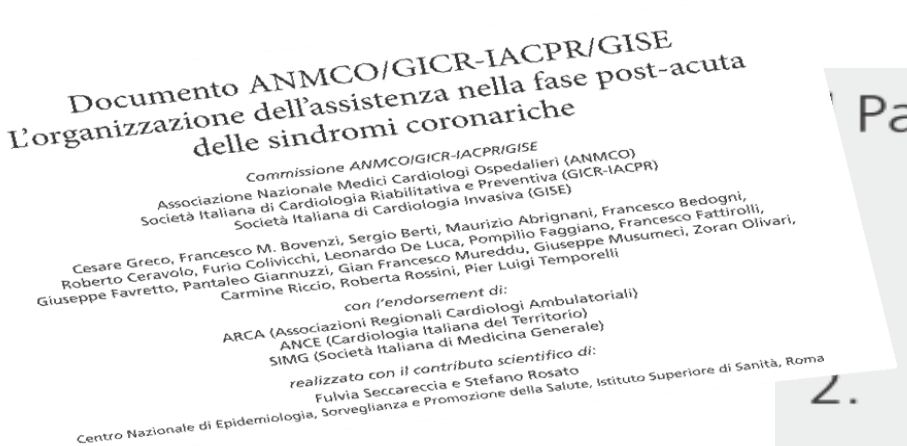
N Engl J Med 2015;373:2103-16.

Il Documento :

AHA/ACC/ASH SCIENTIFIC STATEMENT

Treatment of Hypertension in Patients With Coronary Artery Disease

A Scientific Statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension



Documento ANMCO/GICR-IACPR/GISE
L'organizzazione dell'assistenza nella fase post-acuta delle sindromi coronariche

Commissione ANMCO/GICR-IACPR/GISE
Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO)
Società Italiana di Cardiologia Riabilitativa e Preventiva (GICR-IACPR)
Società Italiana di Cardiologia Invasiva (GISE)

Cesare Greco, Francesco M. Bovenzi, Sergio Berti, Maurizio Abrignani, Francesco Bedogni, Roberto Ceravolo, Furio Colivicchi, Leonardo De Luca, Pompilio Faggiano, Francesco Fattirolli, Giuseppe Favretto, Pantaleo Giannuzzi, Gian Francesco Mureddu, Giuseppe Musumeci, Zoran Olivari, Carmine Riccio, Roberta Rossini, Pier Luigi Temporelli

con l'endorsement di:
ARCA (Associazioni Regionali Cardiologi Ambulatoriali)
ANCE (Cardiologia Italiana del Territorio)
SIMG (Società Italiana di Medicina Generale)

realizzato con il contributo scientifico di:
Fulvia Seccareccia e Stefano Rosato
Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute, Istituto Superiore di Sanità, Roma

Panel ritiene che:

2. in accordo con le indicazioni delle linee guida il target pressorio <140 mmHg, debba essere perseguito in tutti i pazienti con cardiopatia ischemica cronica stabile; tuttavia, in alcuni sottogruppi ad elevato rischio (ipertrofia ventricolare sinistra, disfunzione renale, diabete mellito, disfunzione ventricolare sinistra asintomatica) sia opportuno perseguire un target <130 mmHg, attraverso una titolazione dei farmaci (primariamente betabloccanti e bloccanti del sistema renina-angiotensina) al fine di raggiungere la dose massima tollerata e di individualizzare l'approccio al rischio residuo.

G Ital Cardiol 2014;15(1 Suppl 1):3S-27S


Documento ANMCO/GICR-IACPR/GISE
L'organizzazione dell'assistenza nella fase post-acuta delle sindromi coronariche

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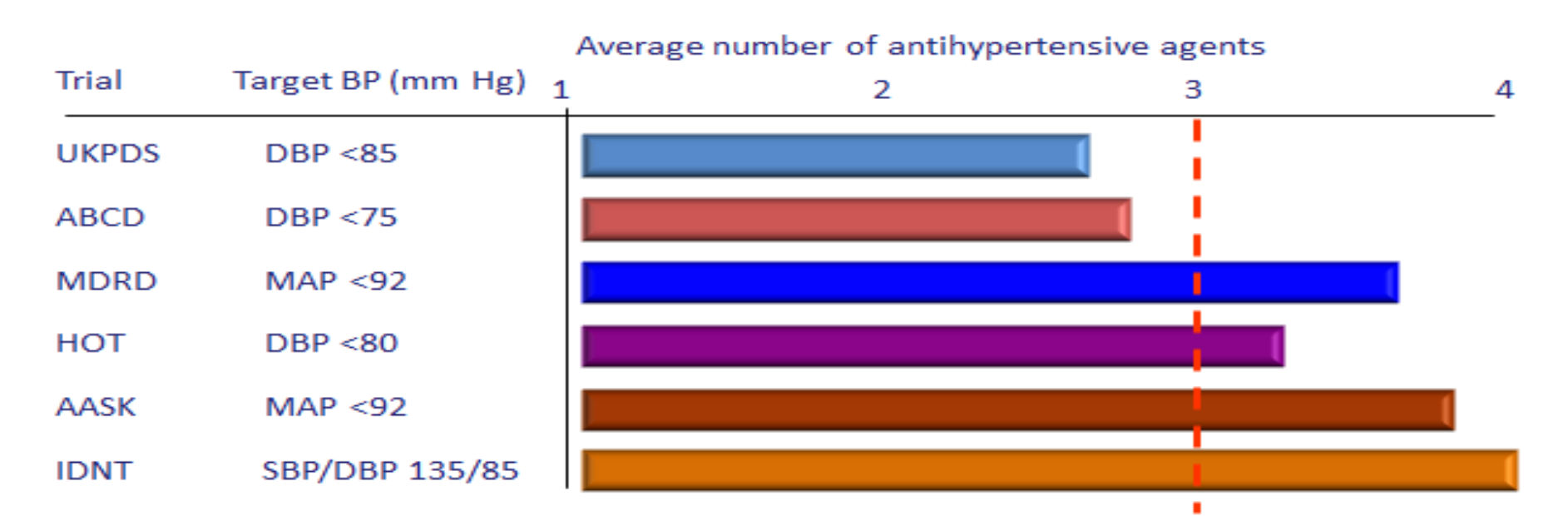
Tabella 3. Obiettivi della terapia farmacologica.

- Assicurarsi che i seguenti trattamenti raccomandati siano stati iniziati alla dimissione e mantenuti in terapia:
  - Doppia antiaggregazione per 12 mesi ☐
  - Statina ad alta efficacia ☐
  - Betabloccante (o ivabradina, se controindicato) ☐
  - ACE-inibitore (o ARB se non tollerato) ☐
  - Omega-3 ☐
  - Antialdosteronico (se disfunzione ventricolare sinistra o scompenso cardiaco) ☐
- Verificare che la titolazione dei farmaci fino al dosaggio raccomandato (o se necessario, l'associazione di più farmaci) consenta di raggiungere e mantenere i seguenti target:
  - Frequenza cardiaca a riposo ≤60/min ☐
  - Pressione arteriosa ≤140/90 mmHg (eventualmente ≤130/80 mmHg) ☐
  - Colesterolo LDL <70 mg/dl (colesterolo non HDL <100 mg/dl) ☐
  - HbA_{1c} <7% ☐
- Verificare l'aderenza alla terapia, alla doppia antiaggregazione in particolare, per il periodo di tempo necessario
- Indicare l'introduzione di nuovi farmaci per la comparsa di sintomi (es. ranolazina per angina, diuretici per dispnea, ecc.)

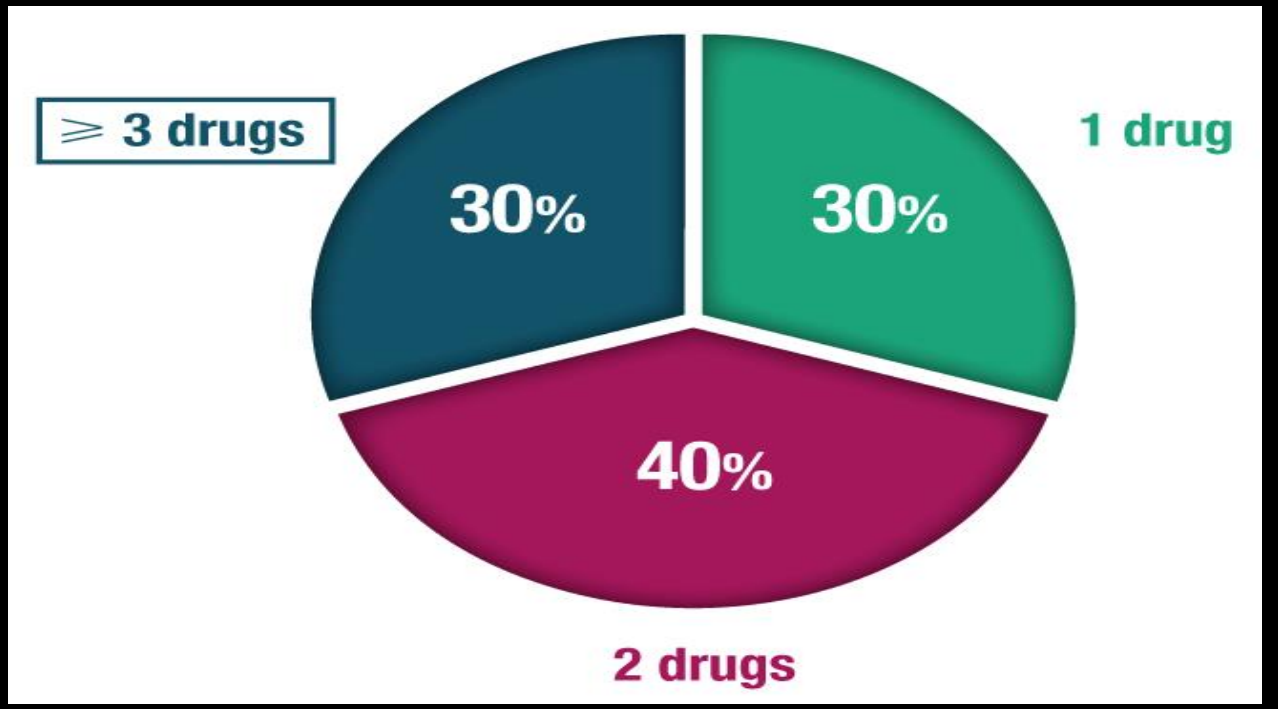
Numero medio di antipertensivi necessari per raggiungere l'obiettivo pressorio



DBP, diastolic BP; SBP, systolic BP; MAP, mean arterial pressure; UKPDS, United Kingdom Prospective Diabetes Study; ABCD, Appropriate Blood Pressure Control in Diabetes; MDRD, Modification of Diet in Renal Disease; HOT, Hypertension Optimal Treatment; AASK, African American Study of Kidney Disease; IDNT, Irbesartan Diabetic Nephropathy Trial

Real Word

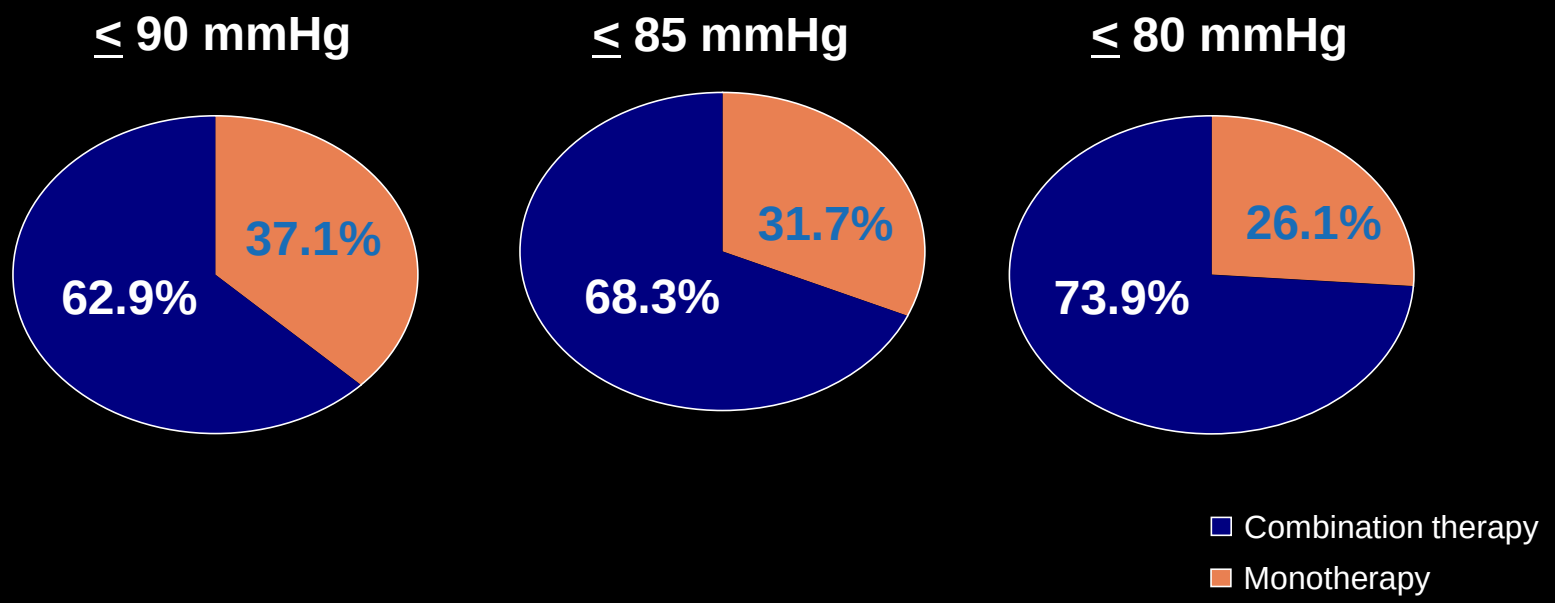
- 1 paziente iperteso su 3 è in trattamento con 3 o più antipertensivi [1]



1.Rappresentazione grafica dei dati presenti nel testo da Thoenes M et al. Antihypertensive drug therapy and blood pressure control in men and women: an international perspective. *J Hum Hypertens*. 2010;24:336-344.

The need for combination therapy

in terms of the target DBP group



The lower the target DBP, the greater the need for combination therapy

Hannsonn L. et al.: Lancet 1998, 351: 1755-62

Cause di insuccesso terapeutico:

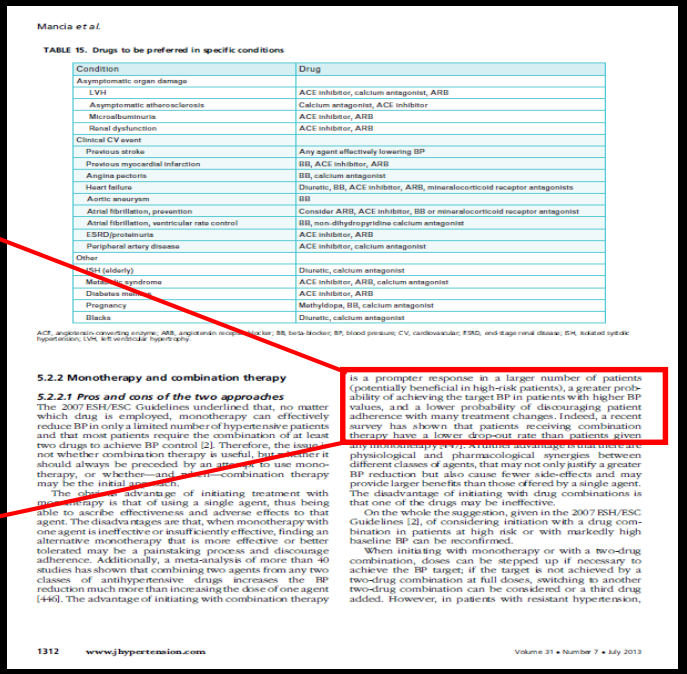
Mancato raggiungimento del controllo pressorio

Scarsa aderenza al trattamento prescritto

Le Linee Guida e le terapie di associazione

Recenti analisi retrospettive hanno dimostrato che iniziare il trattamento con **la terapia di combinazione** consente:

- **Miglior controllo dei valori pressori**
- **Minor incidenza di abbandono della terapia**



Mancia *et al.*

TABLE 15. Drugs to be preferred in specific conditions

Condition	Drug
Asymptomatic organ damage	
LVH	ACE inhibitor, calcium antagonist, ARB
Asymptomatic atherosclerosis	Calcium antagonist, ACE inhibitor
Microalbuminuria	ACE inhibitor, ARB
Renal dysfunction	ACE inhibitor, ARB
Clinical CV event	
Previous stroke	Any agent effectively lowering BP
Previous myocardial infarction	BB, ACE inhibitor, ARB
Angina pectoris	BB, calcium antagonist
Heart failure	Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonists
Aortic aneurysm	BB
Atrial fibrillation, prevention	Consider ARB, ACE inhibitor, BB or mineralocorticoid receptor antagonist
Atrial fibrillation, ventricular rate control	BB, non-dihydropyridine calcium antagonist
ESRD/proteinuria	ACE inhibitor, ARB
Peripheral artery disease	ACE inhibitor, calcium antagonist
Other	
ISH (elderly)	Diuretic, calcium antagonist
Metabolic syndrome	ACE inhibitor, ARB, calcium antagonist
Diabetes mellitus	ACE inhibitor, ARB
Pregnancy	Methyldopa, BB, calcium antagonist
Blacks	Diuretic, calcium antagonist

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, beta-blocker; BP, blood pressure; CV, cardiovascular; ESRD, end-stage renal disease; ISH, isolated systolic hypertension; LVH, left ventricular hypertrophy.

5.2.2 Monotherapy and combination therapy

5.2.2.1 Pros and cons of the two approaches

The 2007 ESH/ESC Guidelines underlined that, no matter which drug is employed, 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 [2]. 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.

The obvious advantage of initiating treatment with monotherapy is that of using a single agent, thus being able to ascribe effectiveness and adverse effects to that agent. The disadvantages are that, when monotherapy with one agent is ineffective or insufficiently effective, finding an alternative monotherapy that is more effective or better tolerated may be a painstaking process and discourage adherence. Additionally, a meta-analysis of more than 40 studies has shown that combining two agents from any two classes of antihypertensive drugs increases the BP reduction much more than increasing the dose of one agent [446]. The advantage of initiating with combination therapy is a prompter response in a larger number of patients (potentially beneficial in high-risk patients), a greater probability of achieving the target BP in patients with higher BP values, and a lower probability of discouraging patient adherence with many treatment changes. Indeed, a recent survey has shown that patients receiving combination therapy have a lower drop-out rate than patients given any monotherapy [447]. Another advantage is that there are physiological and pharmacological synergies between different classes of agents, that may not only justify a greater BP reduction but also cause fewer side-effects and may provide larger benefits than those offered by a single agent. The disadvantage of initiating with drug combinations is that one of the drugs may be ineffective.

On the whole the suggestion, given in the 2007 ESH/ESC Guidelines [2], of considering initiation with a drug combination in patients at high risk or with markedly high baseline BP can be reconfirmed.

When initiating with monotherapy or with a two-drug combination, doses can be stepped up if necessary to achieve the BP target; if the target is not achieved by a two-drug combination at full doses, switching to another two-drug combination can be considered or a third drug added. However, in patients with resistant hypertension,

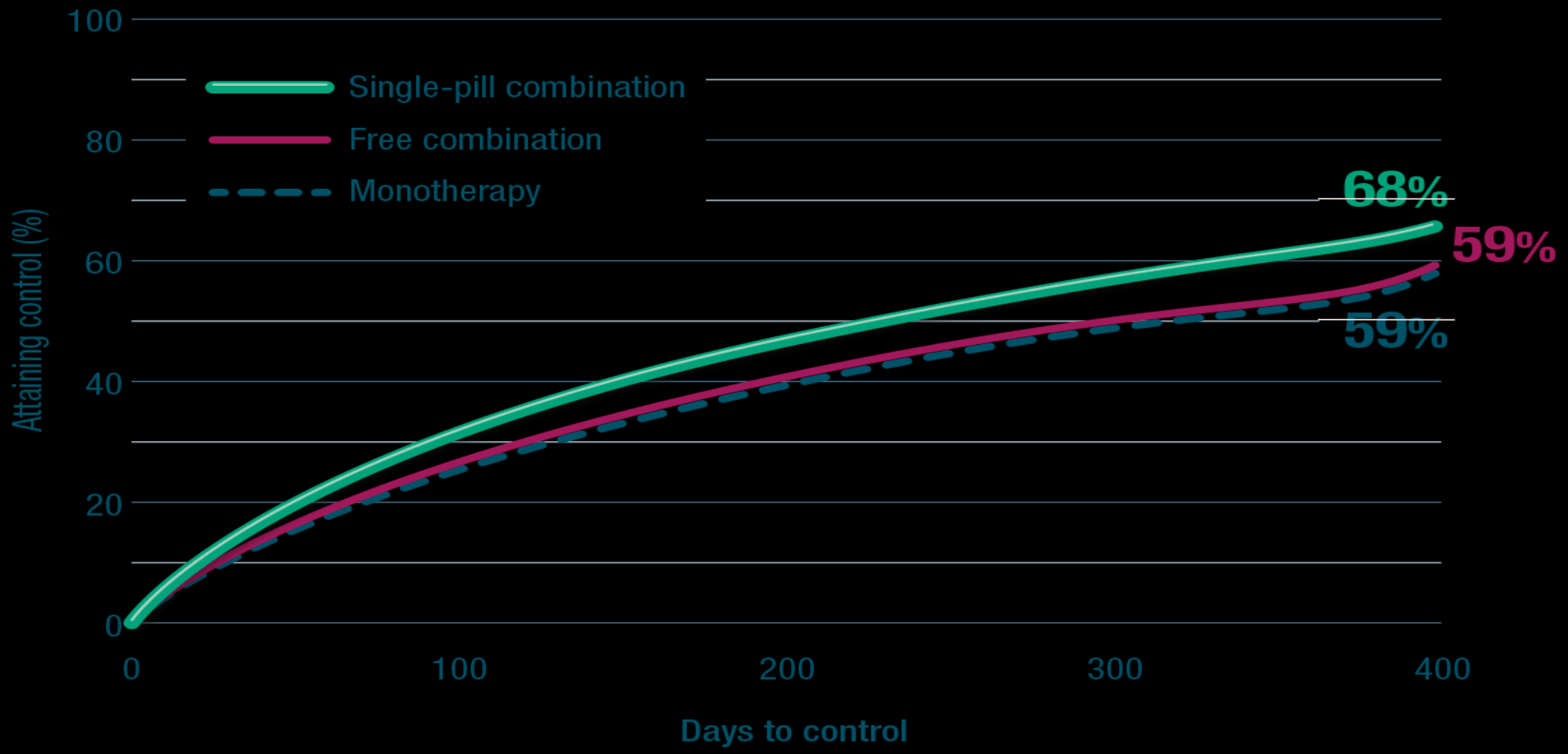
Razionale della terapia di combinazione

L’associazione migliora l’aderenza alla terapia

L’associazione fissa riduce il rischio di non aderenza alla terapia del 24% vs l’associazione libera

Bangalore S et al. Fixed-Dose Combinations Improve Medication Compliance: A Meta-Analysis. *Am J Med.* 2007;120:713-719.

Le associazioni sono più efficaci nel raggiungimento del controllo pressorio vs le associazioni estemporanee [1]



*"Un maggiore utilizzo **dell'associazione può migliorare il controllo dell'ipertensione e degli eventi cardiovascolari** nel primo anno di trattamento"*

Rielaborazione grafica da Egan BM et al.Initial Monotherapy and Combination Therapy and Hypertension Control the First Year. *Hypertension*. 2012;59:1124-1131.

Scelta razionale da combinare

Efficacia antipertensiva

Capacità di migliorare la prognosi

Blood pressure goals in hypertensive patients*

Recommendations	Class	Level
A systolic BP goal of <140 mmHg:		
a) is recommended in patients at low-moderate CV risk,	I	B
b) is recommended in patients with diabetes,	I	A
c) should be considered in patients with previous stroke or TIA,	IIa	B
d) should be considered in patients with coronary heart disease,	IIa	B
e) should be considered in patients with diabetic or non-diabetic chronic kidney disease.	IIa	B
A diastolic BP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated.	I	A

*See dedicated section for recommendations in special conditions and populations

www.escardio.org/guidelines

Eur Heart J, 2013; 34: 2159-2219
J Hypertens, 2013; 31: 1281-1357
Blood Pressure, 2013: 193-278

European Society of Hypertension

EUROPEAN SOCIETY OF CARDIOLOGY®

Linee Guida e terapia di associazione

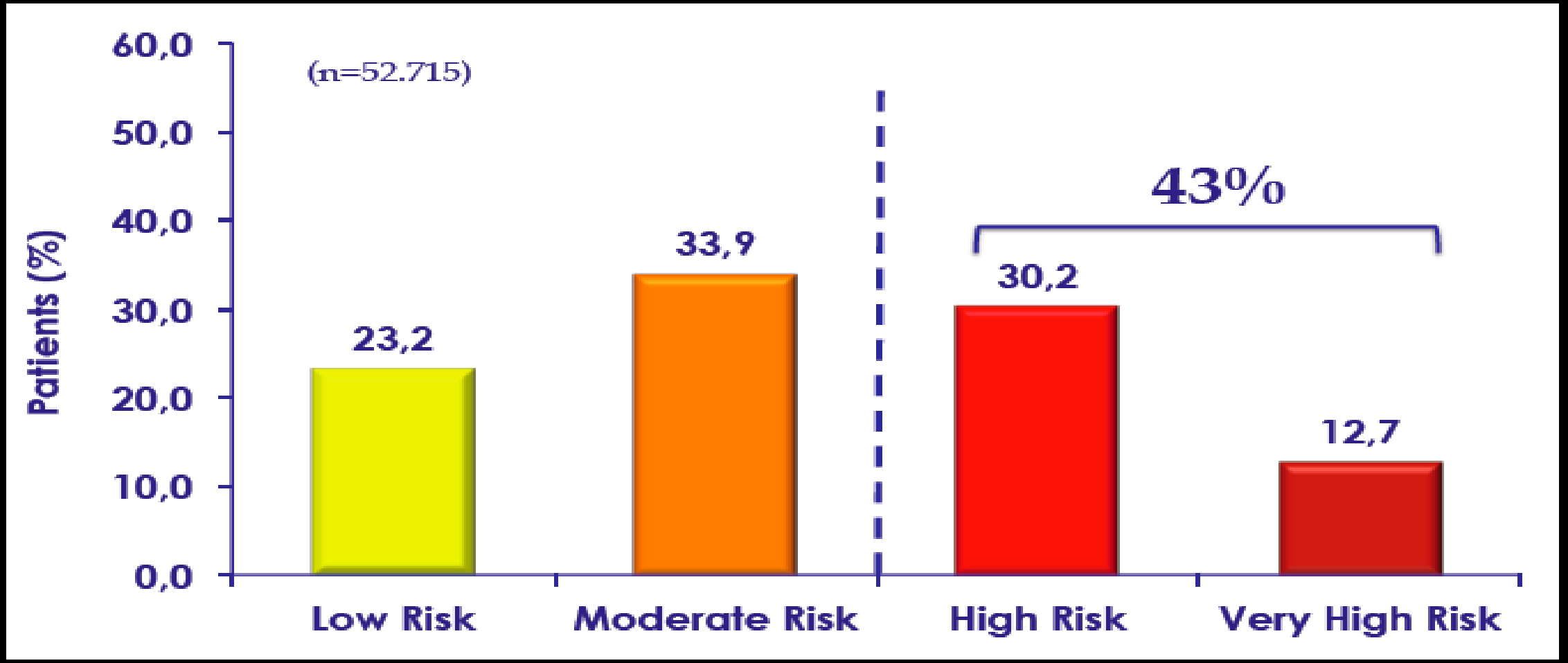
Le linee guida suggeriscono come prioritario l'impiego di combinazioni fisse di farmaci di maggiore efficacia e più redditizie in termini di prevenzione cardiovascolare

Le associazioni raccomandate dovrebbero essere somministrate sotto forma di una singola compressa con dose fisse dei principi attivi

Razionale della terapia di combinazione

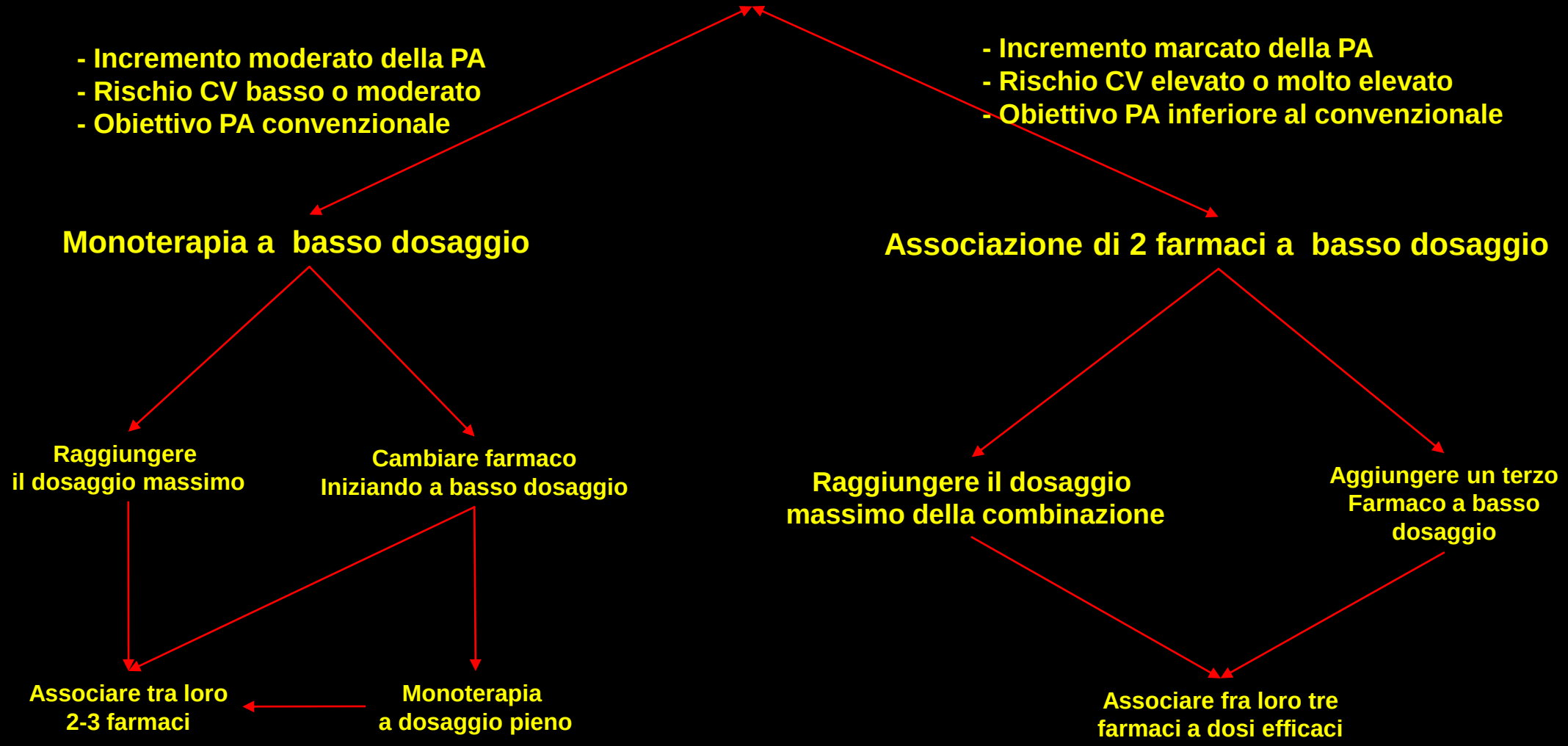
La terapia di associazione iniziale rappresenta la strategia di elezione nei soggetti che presentano una maggior gravità del quadro ipertensivo (grado 2-3) e ed un profilo di rischio cv elevato

La metà degli ipertesi sono a rischio CV alto o molto alto



Volpe M, et al. J Hypertension 2007;25(7):1491-8

Criteri di scelta tra monoterapia e terapia di associazione



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 hanno 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 collaterali indesiderati

Associazione ideale secondo le linee Guida

- l'efficacia dell'associazione in termini di controllo della pressione arteriosa
- Controllo a lungo termine della pressione arteriosa nelle 24 h
- un'adeguata tollerabilità soggettiva
- l'evidenza di una riduzione della morbilità cardiovascolare

Le associazioni razionali sono realizzate tenendo conto del meccanismo d' azione dei farmaci antipertensivi

Diuretici
Calcio antagonisti
Alfa-antagonisti

↑ SRA ↓

ACE-inibitori
AT-1 antagonisti
Beta-bloccanti

Vasodilatatori

↑ SNS ↓

ACE-inibitori
AT-1 antagonisti
Beta-bloccanti
Simpatomodulatori

Associazioni di farmaci antipertensivi non razionali o potenzialmente pericolose

Farmaci senza effetto additivo

- Diuretico + Calcio-antagonista
- Beta-bloccante + ACE-inibitore o AT1-antagonista
- ACE-inibitore + AT1-antagonista

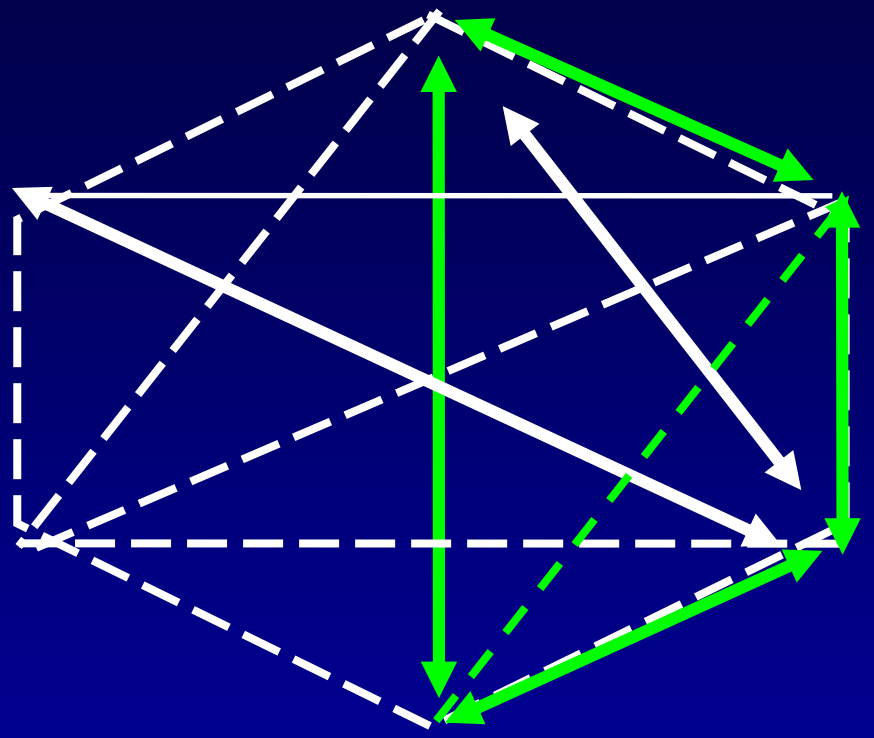
Farmaci con interazione negativa sull'effetto ipotensivo

- Alfa-1 antagonista + Clonidina

Associazioni potenzialmente pericolose

- Beta-bloccante + Clonidina
- Beta-bloccante + Calcio-antagonista non diidropiridinico

Possibili combinazioni fra diverse classi di farmaci antiipertensivi



- LE COMBINAZIONI DA PREFERIRE NELLA POPOLAZIONE IPERTESA SONO ESPRESSE CON LINEE VERDI
- I RIQUADRI SI RIFERISCONO ALLE CLASSI DI FARMACI ANTIPERTENSIVI I CUI BENEFICI SONO STATI DIMOSTRATI DA TRIAL CLINICI DI INTERVENTO

Linee Guida ESH/ESC 2007

Le associazioni sono tutte uguali?

ACE/ARB-diuretico
ACE/ARB-calcioantagonista
ACE/calcioantagonista/diuretico

2013 ESC guidelines on the management of stable coronary artery disease

European Heart Journal (2013) **34**, 2949–3003
doi:10.1093/eurheartj/eht296

The Task Force on the management of stable coronary artery disease of the European Society of Cardiology

However, not all clinical trials have demonstrated that the ACE inhibitors reduce all-cause mortality, CV mortality, non-fatal MI, stroke and heart failure in patients with atherosclerosis and preserved LV function.[351,352,355] In SCAD patients with hypertension, a combination therapy consisting of an ACE inhibitor and a DHP CCB, such as perindopril/amlodipine in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) trial and benazepril/amlodipine in the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial, is preferred.[356,357] In contrast, adding an angiotensin II receptor antagonist (ARB) to an ACE inhibitor was associated with more adverse events, without an increase in benefit.[358,359]

Linee Guida Europee CAD: Perindopril/Amlodipina da preferire rispetto alla associazione ace-inibitore-diuretico


European Heart Journal Advance Access published August 30, 2013

ESC GUIDELINES

2013 ESC guidelines on the management of stable coronary artery disease

*"**In pazienti Ipertesi ad elevato rischio CV** (SCAD), **è da preferire la terapia di** associazione con ACE-Inibitore ed un Calcio Antagonista diidropiridinico, come ad esempio **Perindopril/Amlodipina** nello studio ASCOT e Benazepril/Amlodipina nello studio ACCOMPLISH."*[1]

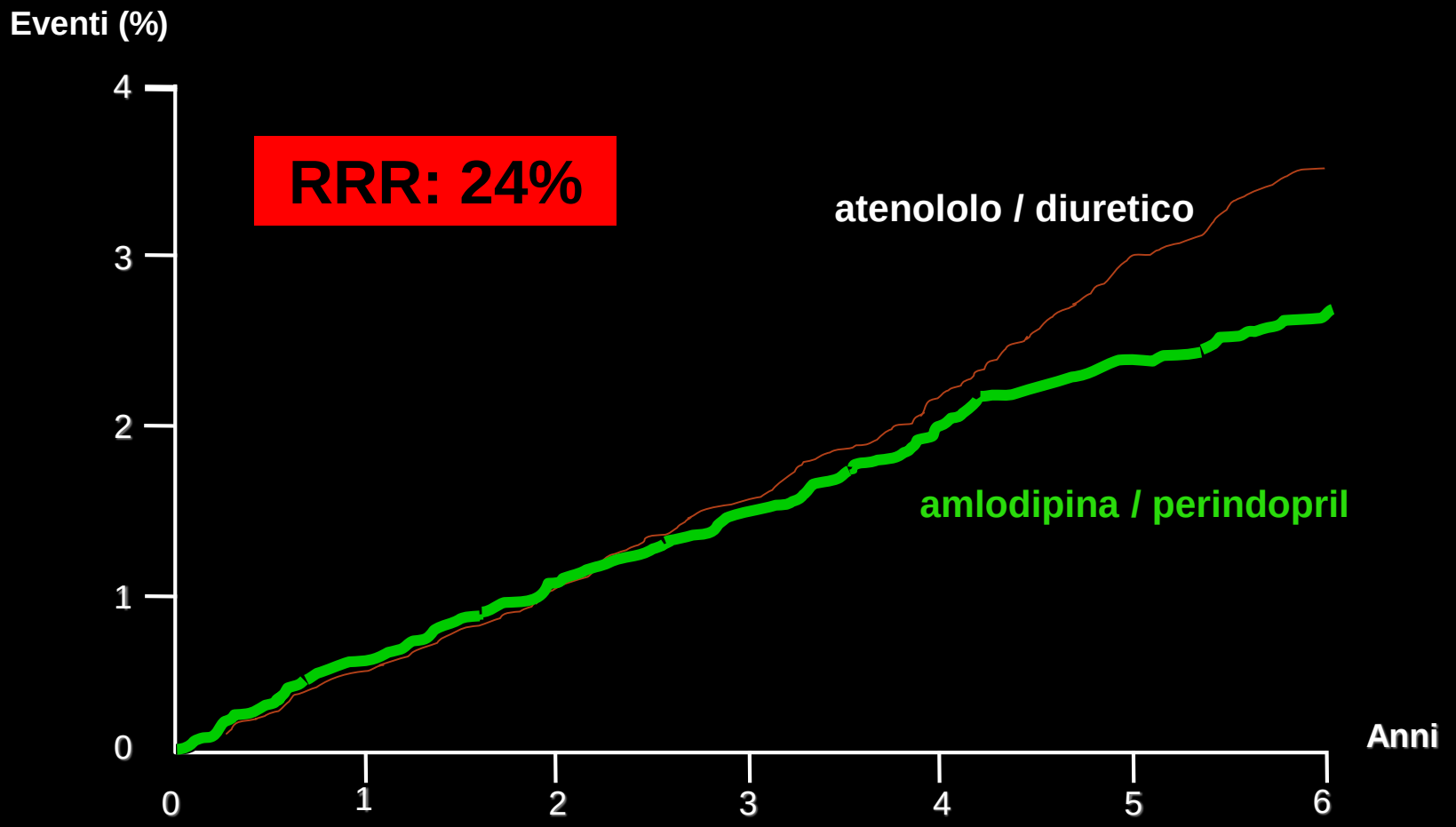
UNICA ASSOCIAZIONE CON LA SPECIFICA INDICAZIONE IN RCP

-27%
INFARTI[2]

1.ESC Guidelines SCAD European Heart Journal dor:10,1093/eurheartj/eht296
2.Micheal E.Bertrand et al., on behalf of the EUROPA Investigators, American Health Journal, May 2010

Risultati End-points

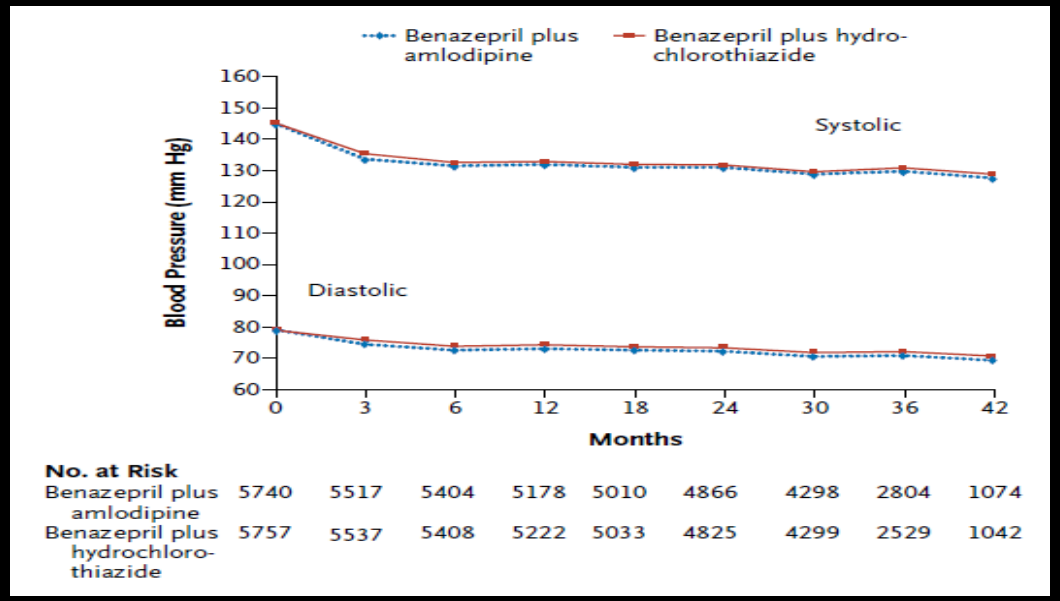
Mortalità cardiovascolare



Mortalità totale
-11%

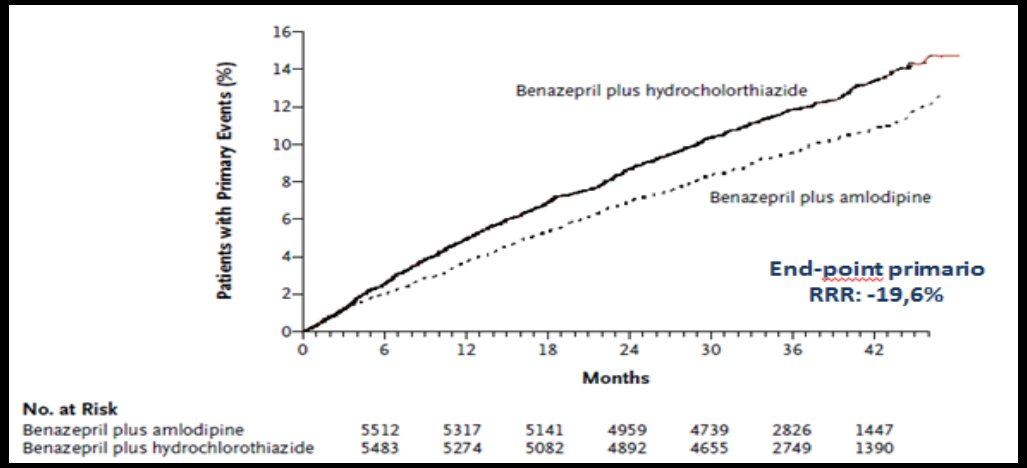
ASCOT Collaborative Group. Lancet. 2005;366:895-906

RISULTATI STUDIO ACCOMPLISH



Riduzioni pressorie simili nei valori sistolici e diastolici

End-point primario:
evento cardiovascolare + mortalità per cause cardiovascolari:
ACE-I/Ca-Antagonista -19,6% vs ACE-I/Diuretico



STUDIO ACCOMPLISH

Lo studio dimostra:

la significativa superiorità dell'associazione ACE-I/Ca-Antagonista rispetto all'ACE-inibitore diuretico

LINEE GUIDA EUROPEE IPERTENSIONE

that diuretics (including thiazides, chlorthalidone and indapamide), beta-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations. However, some therapeutic issues that have recently been raised are discussed below.

5.2.1.1 Beta-blockers

The reasons why, at variance from some guidelines, beta-blockers were maintained as a possible choice for antihypertensive treatment were summarized in the 2007 ESH/ESC Guidelines and further discussed in the 2009 re-appraisal document [2,141]. Although acknowledging that the quality of the evidence was low, a Cochrane meta-analysis (substantially reproducing a 2006 meta-analysis by the same group) [395,397] has reported that beta-blockers may be inferior to some—but not all—other drug classes for some outcomes. Specifically, they appear to be worse than calcium antagonists (but not diuretics and RAS blockers) for total mortality and CV events, worse than calcium antagonists and RAS blockers for stroke and equal to calcium antagonists, RAS blockers and diuretics for CHD. On the other hand, the large meta-analysis by Law *et al.* has shown beta-blocker-initiated therapy to be (i) equally as effective as the other major classes of antihypertensive agents in preventing coronary outcomes and (ii) highly effective in preventing CV events in patients with a recent myocardial infarction and those with heart failure [284]. A similar incidence of CV outcomes with beta-blockers and/or diuretics or their combinations compared with other drug classes has also been reported in the meta-analysis of the BP-lowering treatment trialists' collaboration [394].

A slightly lower effectiveness of beta-blockers in preventing stroke [284] has been attributed to a lesser ability to reduce central SBP and pulse pressure [398,399]. However, a lower effectiveness in stroke prevention is also shared by ACE inhibitors [284], although these compounds have been reported to reduce central BP better than beta-blockers [398]. Beta-blockers also appear (i) to have more side-effects (although the difference with other drugs is less pronounced in double blind studies) [400] and (ii) to be somewhat less effective than RAS blockers and calcium antagonists in regressing or delaying OD, such as LVH, carotid IMT, aortic stiffness and small artery remodelling [141]. Also, beta-blockers tend to increase body weight [401] and, particularly when used in combination with diuretics, to facilitate new-onset diabetes in predisposed patients [402]. This phenomenon may have been overemphasized by the fact that all trial analyses have been limited to patients free of diabetes or with glucose <7.0 mmol/L, ignoring the fact that a noticeable number of patients with a diagnosis of diabetes at baseline do not have this diagnosis reconfirmed at study end, which obviously reduces the weight of treatment-induced diabetes and raises doubts about the precision of the definition of diabetes used in the above analyses [403]. Some of the limitations of traditional beta-blockers do not appear to be shared by some of the vasodilating beta-blockers, such as celiprolol, carvedilol and nebivolol—more widely used today—which reduce central pulse pressure and aortic stiffness better than atenolol or metoprolol [404–406] and affect insulin sensitivity less than metoprolol [407,408]. Nebivolol has recently been shown not to worsen glucose tolerance compared with placebo and when added to hydrochlorothiazide [409]. Both carvedilol and nebivolol have been favourably tested in RCTs, although in heart failure rather than arterial hypertension [410]. Finally, beta-blockers have recently been reported not to increase, but even reduce, the risk of exacerbations and to reduce mortality in patients with chronic obstructive lung disease [411].

5.2.1.2 Diuretics

Diuretics have remained the cornerstone of antihypertensive treatment since at least the first Joint National Committee (JNC) report in 1977 [412] and the first WHO report in 1978 [413], and still, in 2003, they were classified as the only first-choice drug by which to start treatment, in both the JNC-7 [264] and the WHO/International Society of Hypertension Guidelines [95,264]. The wide use of thiazide diuretics should take into account the observation in the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial [414] that their association with an ACE inhibitor was less effective in reducing CV events than the association of the same ACE inhibitor with a calcium antagonist. The interesting [illegible] but need replication, because no other randomized study has shown a significant superiority of a calcium antagonist over a diuretic. Therefore, the evidence provided by ACCOMPLISH does not appear to bear sufficient weight to exclude diuretics from first-line choice.

It has also been argued that diuretics such as chlorthalidone or indapamide should be used in preference to conventional thiazide diuretics, such as hydrochlorothiazide [271]. The statement that 'There is limited evidence confirming benefit of initial therapy on clinical outcomes with low doses of hydrochlorothiazide' [271] is not supported by a more extensive review of available evidence [332,415]. Meta-analyses claiming that hydrochlorothiazide has a lesser ability to reduce ambulatory BP than other agents, or reduces outcomes less than chlorthalidone [416,417], are confined to a limited number of trials and do not include head-to-head comparisons of different diuretics (no large randomized study is available). In the Multiple Risk Factor Intervention Trial (MRFIT), chlorthalidone and hydrochlorothiazide were not compared by randomized assignment and, overall, chlorthalidone was used at higher doses than hydrochlorothiazide [418]. Therefore no recommendation can be given to favour a particular diuretic agent.

Spironolactone has been found to have beneficial effects in heart failure [419] and, although never tested in RCTs on hypertension, can be used as a third- or fourth-line drug (see Section 6.14) and helps in effectively treating undetected cases of primary aldosteronism. Eplerenone has also shown a protective effect in heart failure and can be used as an alternative to spironolactone [420].

5.2.1.3 Calcium antagonists

Calcium antagonists have been cleared from the suspicion of causing a relative excess of coronary events by the same

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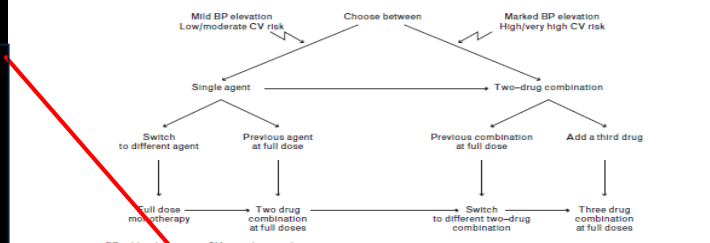

FIGURE 3 Monotherapy vs. drug combination strategies to achieve target BP. Moving from a less intensive to a more intensive therapeutic strategy should be done whenever BP target is not achieved.

adding drugs to drugs should be done with attention to results and any compound overtly ineffective or minimally effective should be replaced, rather than retained in an automatic step-up multiple-drug approach (Fig. 3).

5.2.2.2 Preferred drug combinations

Only indirect data are available from randomized trials giving information on drug combinations effective in reducing CV outcomes. Among the large number of RCTs of antihypertensive therapy, only three systematically used a given two-drug combination in at least one arm: the ADVANCE trial compared an ACE inhibitor and diuretic combination with placebo (but on top of continued background therapy) [276], FEVER compared a calcium antagonist and diuretic combination with diuretic alone (plus placebo) [269] and ACCOMPLISH compared the same ACE inhibitor in combination with either a diuretic or a calcium antagonist [414]. In all other trials, treatment was initiated by monotherapy in either arm and another drug (and sometimes more than one drug) was added in some patients. In some trials, the second drug was chosen by the investigator among those [illegible] used in the other treatment arms, as in Antihypertensive and Lipid-Lowering Treatment to Prevent Heart ATtack (ALLHAT) [448].

With this important reservation, Table 16 shows that, with the exception of an angiotensin receptor blocker and a calcium antagonist (never systematically used in an outcome trial), all combinations were used in at least one active arm of placebo-controlled trials in which the active arm was associated with significant benefit [269,276,287,296,449–454]. In trials comparing different regimens, all combinations have been used in a larger or smaller proportion of patients, without major differences in benefits [186,445,448,455,456,458–461]. The only exceptions are two trials in which a large proportion of the patients received either an angiotensin receptor blocker-diuretic combination or a calcium antagonist-ACE inhibitor combination [423,457], both of which were superior to a beta-blocker-diuretic combination in reducing CV events. Admittedly, a beta-blocker-diuretic combination was as effective as other combinations in several other trials [448,455,460,461], and more effective than placebo in three trials [449,453,454]. However, the beta-blocker- diuretic combination appears to elicit more cases of new-onset diabetes in susceptible individuals, compared with other combinations [462].

[illegible] patients (ACCOMPLISH) [414] found significant superiority of an ACE inhibitor-calcium antagonist combination over the ACE inhibitor-diuretic combination despite there being no BP difference between the two arms. These unexpected results deserve to be repeated, because trials comparing a calcium antagonist-based therapy with a diuretic-based [illegible] antagonist. Nonetheless, the possibility that ACCOMPLISH results may be due to a more effective reduction of central BP by the association of an RAS blocker with a calcium antagonist deserves to be investigated [398,399,464].

The only combination that cannot be recommended on the basis of trial results is that between two different

La minore efficacia dell'associazione ACE-I/diuretico nella riduzione degli eventi cardiovascolari rispetto all'associazione del medesimo ACE-I associato al Ca-Antagonista

Linee Guida e terapia di associazione

Rafforzano il concetto della necessità di un iter diagnostico accurato prima di intraprendere la terapia e dell'importanza di un ricorso più assiduo alla terapia di associazione

"ricorrere alla terapia di associazione ove possibile sotto forma di combinazione fissa di farmaci…privilegiando classi di farmaci che associano una evidente compatibilità reciproca ..

Per ottenere un efficace controllo della pressione arteriosa e con un miglioramento del profilo di rischio cardiovascolare"

La terapia dell’ipertensione è una sfida giornaliera nei nostri ambulatori.
Non esiste il farmaco che va bene a tutti
Bisogna partire col passo giusto anche per dare sicurezza al paziente
In questa ottica le associazioni precostituire rivestono
un ruolo fondamentale.

Lo studio ADVANCE CCB

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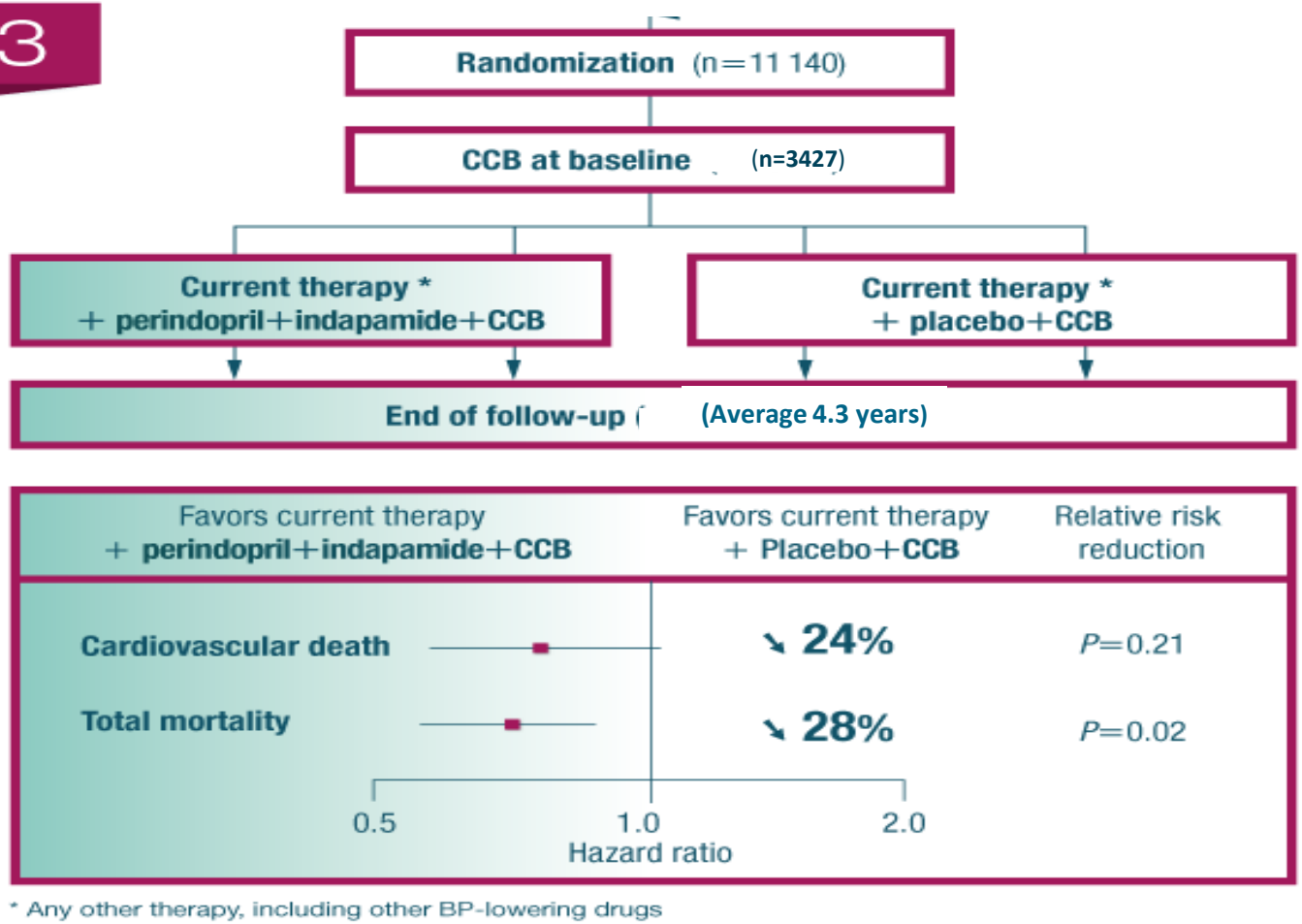

* Any other therapy, including other BP-lowering drugs

Baseline treated for hypertension: 68.3% active drug; 69.2% placebo

1) Rappresentazione grafica dei dati presenti nel testo da Chalmers J, et al; Effects of Combination of Perindopril, Indapamide, and Calcium Channel Blockers in Patients With Type 2 Diabetes Mellitus. Results From the Action in Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation (ADVANCE) Trial. ADVANCE Collaborative Group; *J Hypertens*. 2013;31(Suppl A):e110