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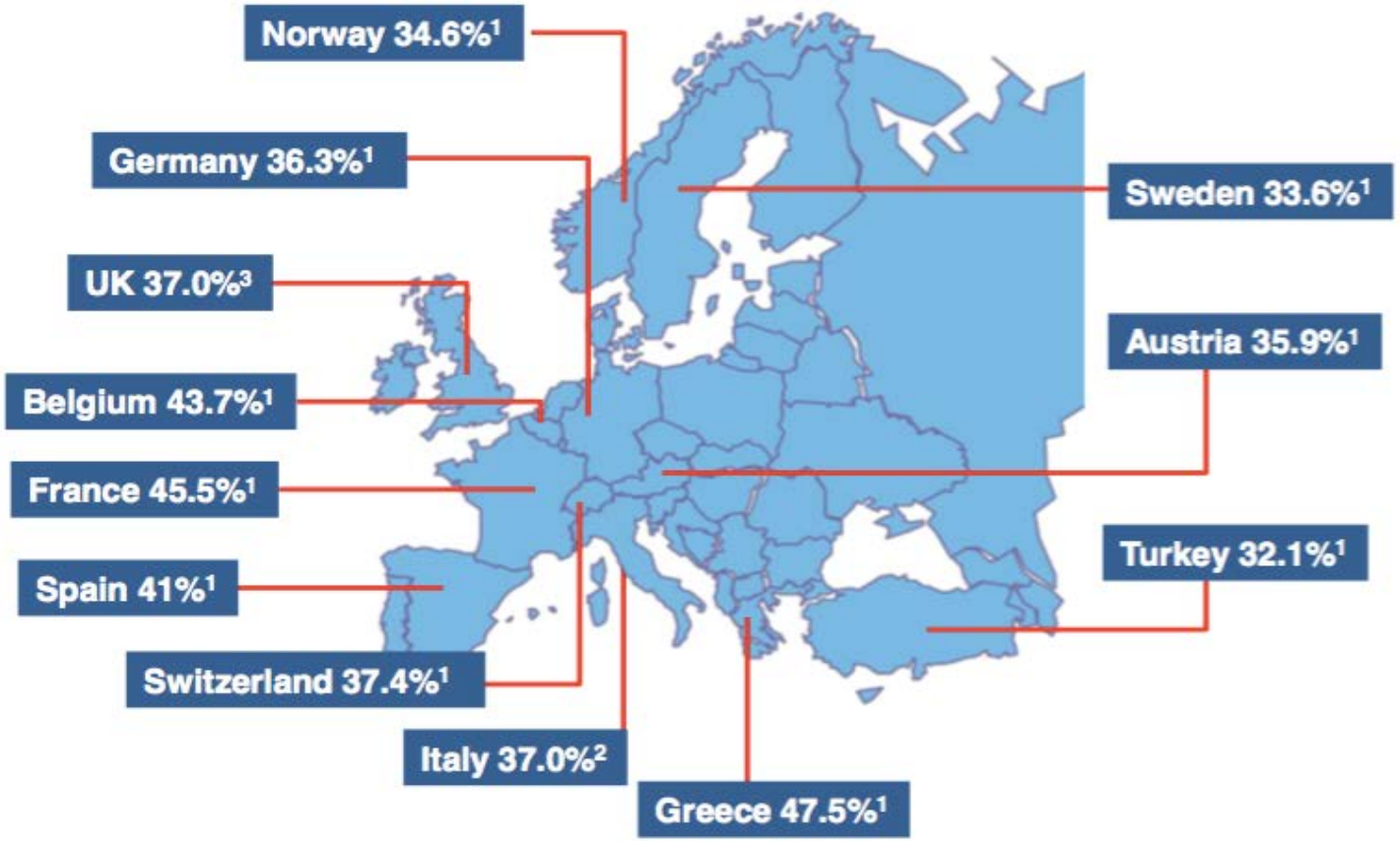
Conflict of Interest Statement

Massimo Volpe **E: massimo.volpe@uniroma1.it**

Title	MD, Full Professor of Cardiology, FESC, FAHA
Current Occupation	University of Rome Sapienza, Department of Clinical and Molecular Medicine
Current Grants	Award University of Rome Sapienza, PRIN Italian Ministry of Health
Speakers' Bureau	Menarini International, Daiichi-Sankyo Europe
Royalties/Activities	None
Consultant/Advisory Board	Takeda International, Daiichi-Sankyo Europe, Actelion, Novartis Pharma
Other Activities	Reviewer ESH/ESC Hypertension Guidelines and ESC CV Prevention Guidelines Past-President of the Italian Society of Hypertension (SIIA) Past-President of the Italian Society of Cardiovascular Prevention (SIPREC)

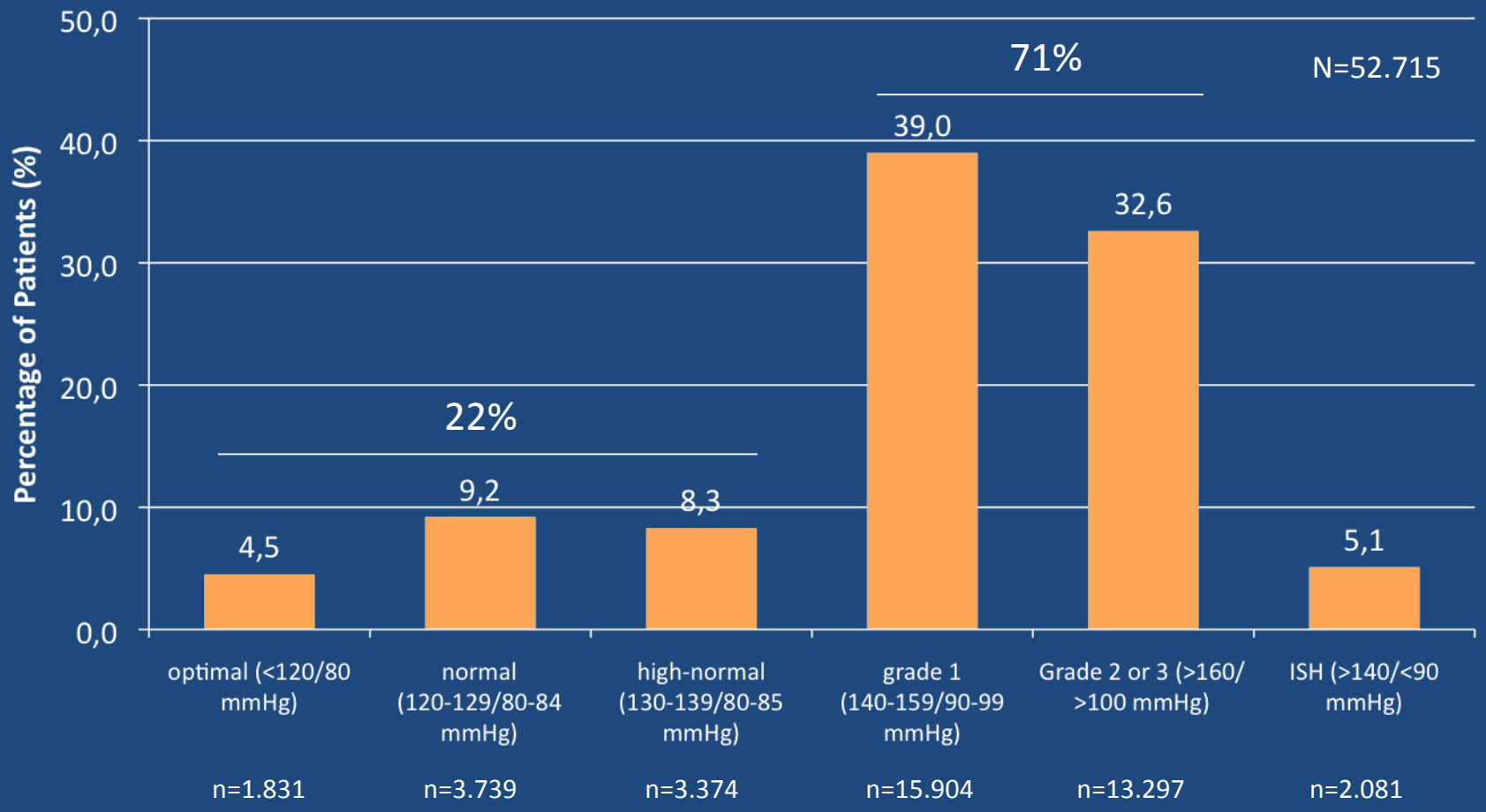
Hypertension Control in Europe



1. Proportion (%) of primary care patients with SBP/DBP <140/90 mmHg (<130/80 mmHg for diabetics)
2. Proportion (%) of patients (mainly in primary care) with SBP/DBP <140/90 mmHg

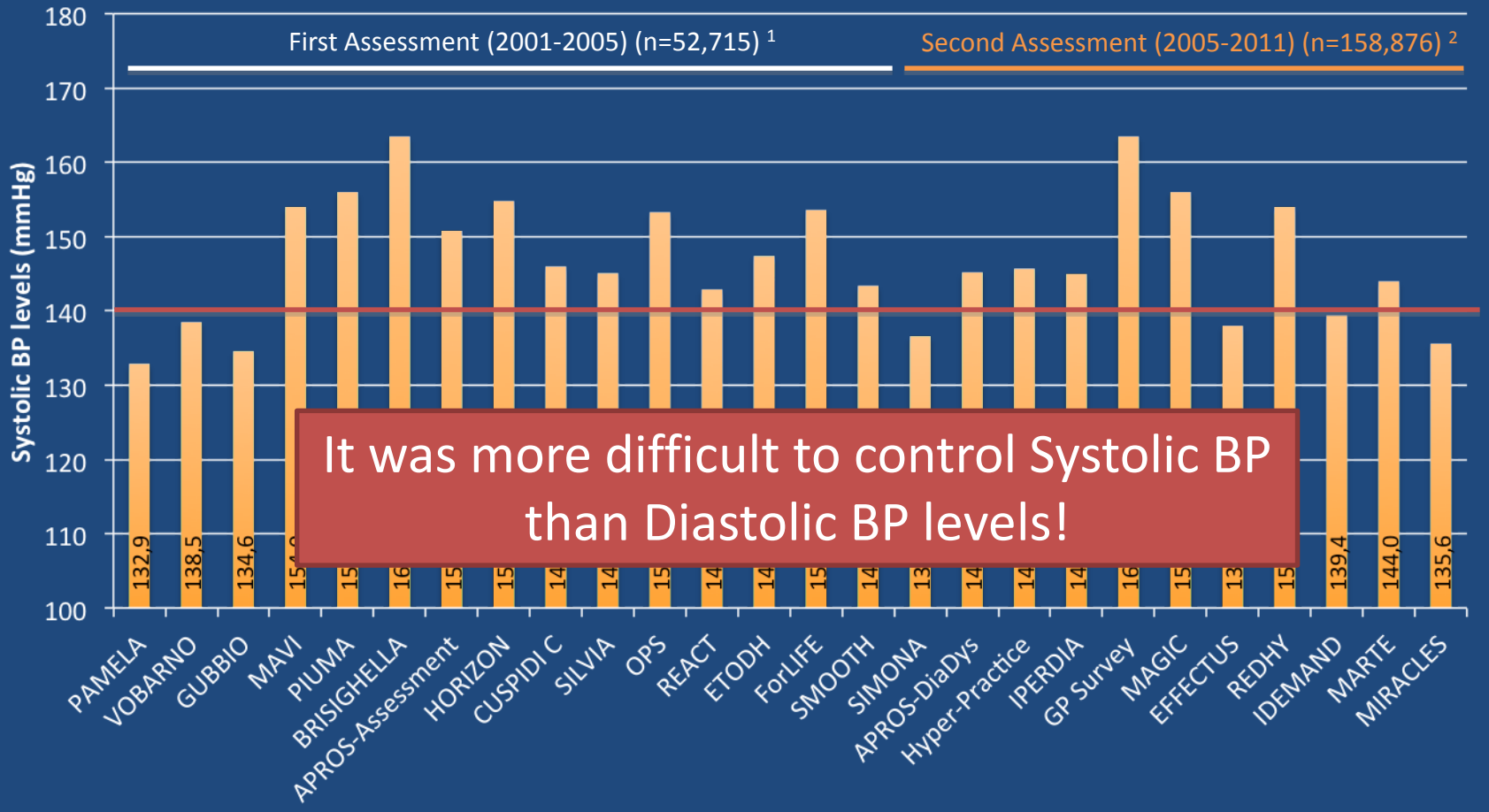
1. Banegas et al. *Eur Heart J* 2011;32:2143–522.
2. Tocci et al. *J Hypertens* 2012;30:1065–74,
3. Falaschetti et al. *Lancet* 2014;383:1912–19

BP Stratification in Hypertensive Patients enrolled in Hypertension Surveys in Italy



Volpe M, Tocci G, et al. J Hypertens 2007 Jul;25(7):1491-8

Systolic BP levels in Patients included in Hypertension Surveys performed in Italy between 2001-2011

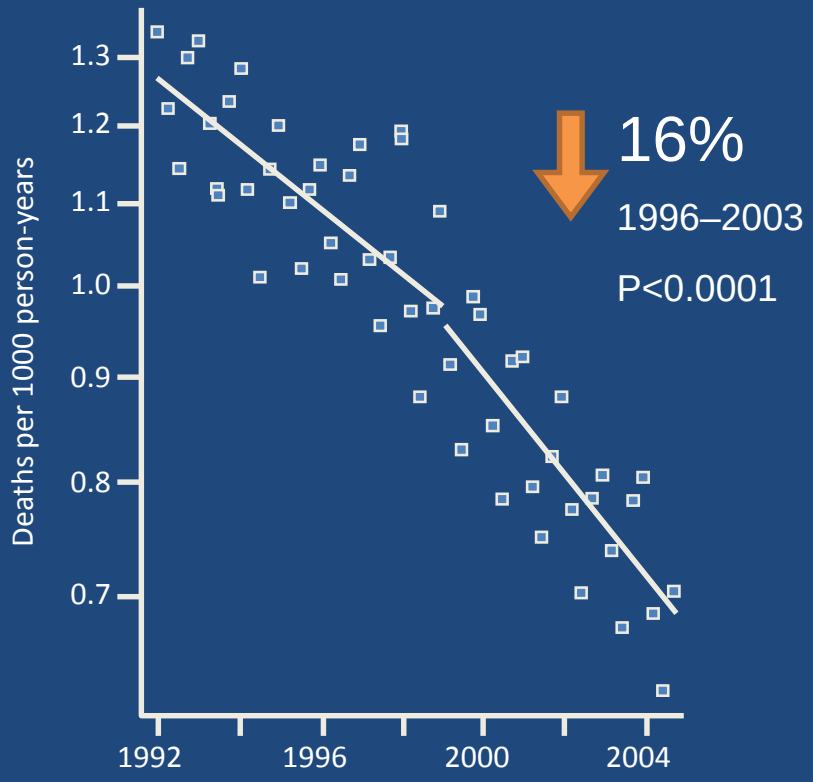


1. Volpe M, Tocci G, et al. J Hypertens 2007;25(7):1491-8.
2. Tocci G, Volpe M, et al. J Hypertens 2012;30:1065-74.

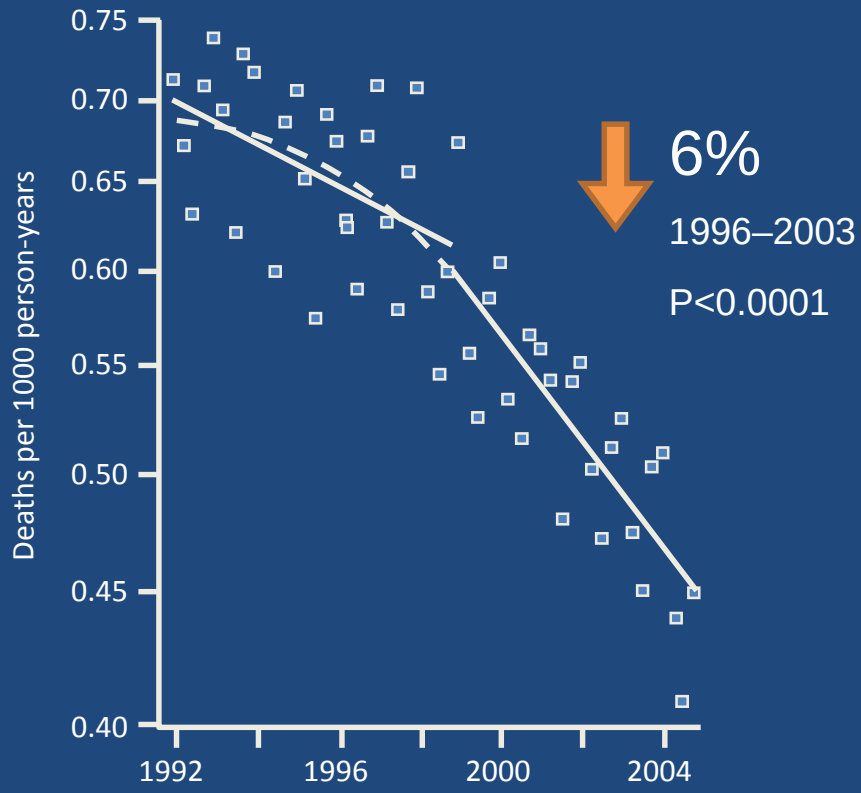
Tocci G, Volpe M, et al. J Hum Hypertens 2015:1-6

Improved hypertension management in Canada has been associated with major benefits

Deaths from acute myocardial infarction



Deaths from stroke



Campbell et al. Hypertension 2009;53:128–34

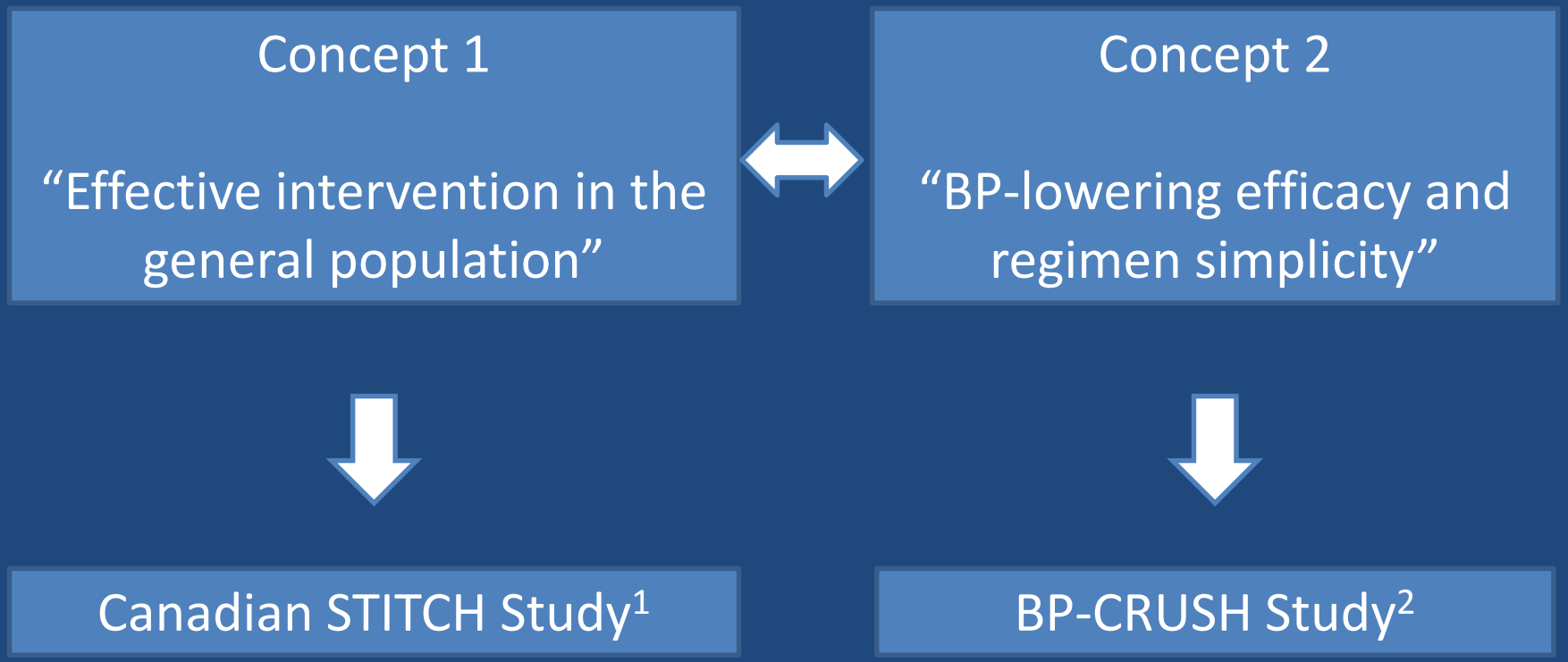
Strategies for improving BP control rates in hypertensive populations

- Various educational, interventional and therapeutic initiatives have been planned and applied in several Countries in line with the Italian Objective 70%.

- These interventions are devoted both to hypertensive patients and to treating physicians to try to reduce the gap between perceived and attained BP control rates in the general population.

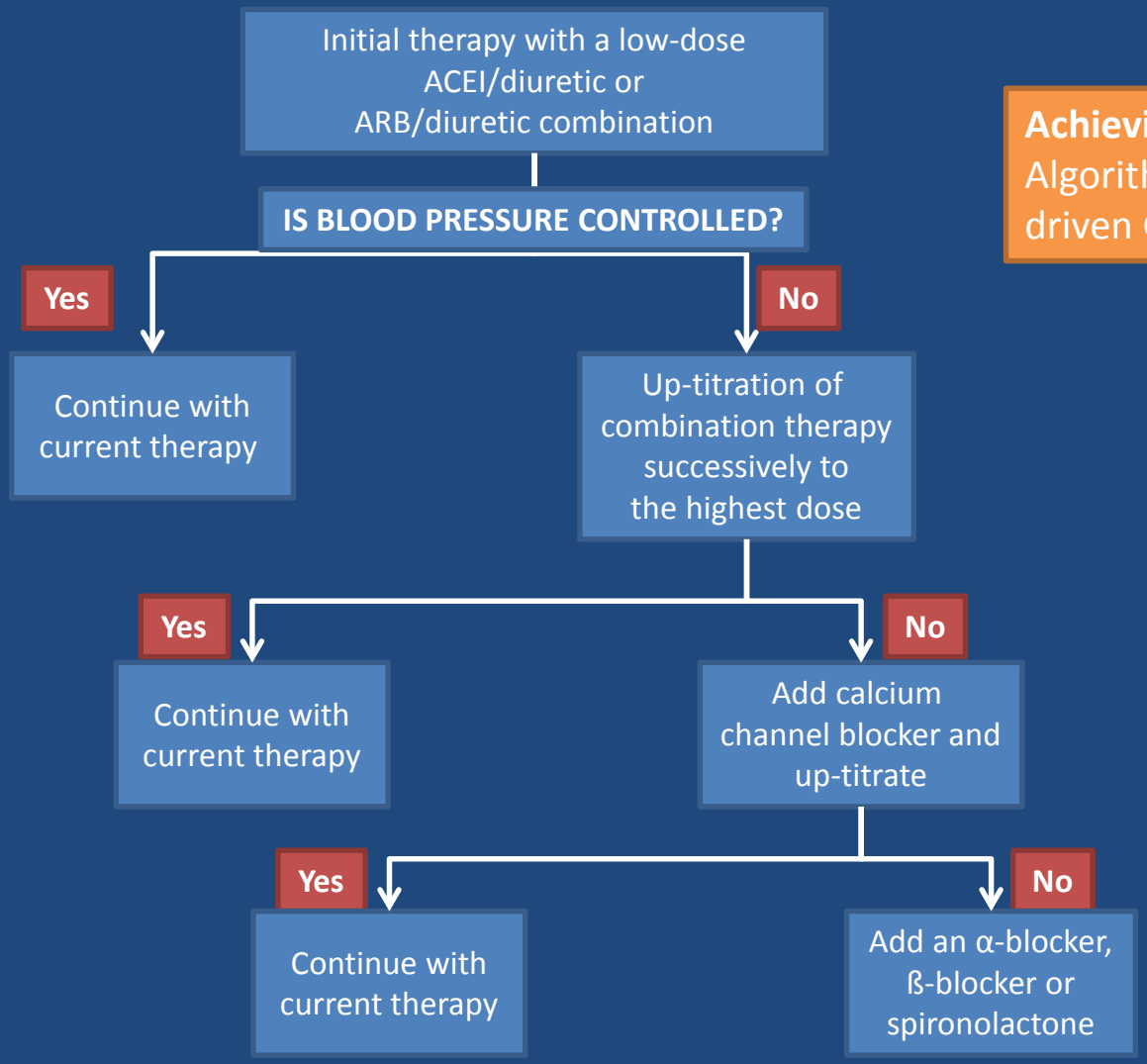
- The evaluation of the effectiveness of these interventions will be part of the predefined outcomes of the Objective 70% program.

Strategies to Improve BP control



1. Feldman et al. Hypertens 2009;53:646–53
2. Weir et al. J Clin Hypertens 2011;13:404–12

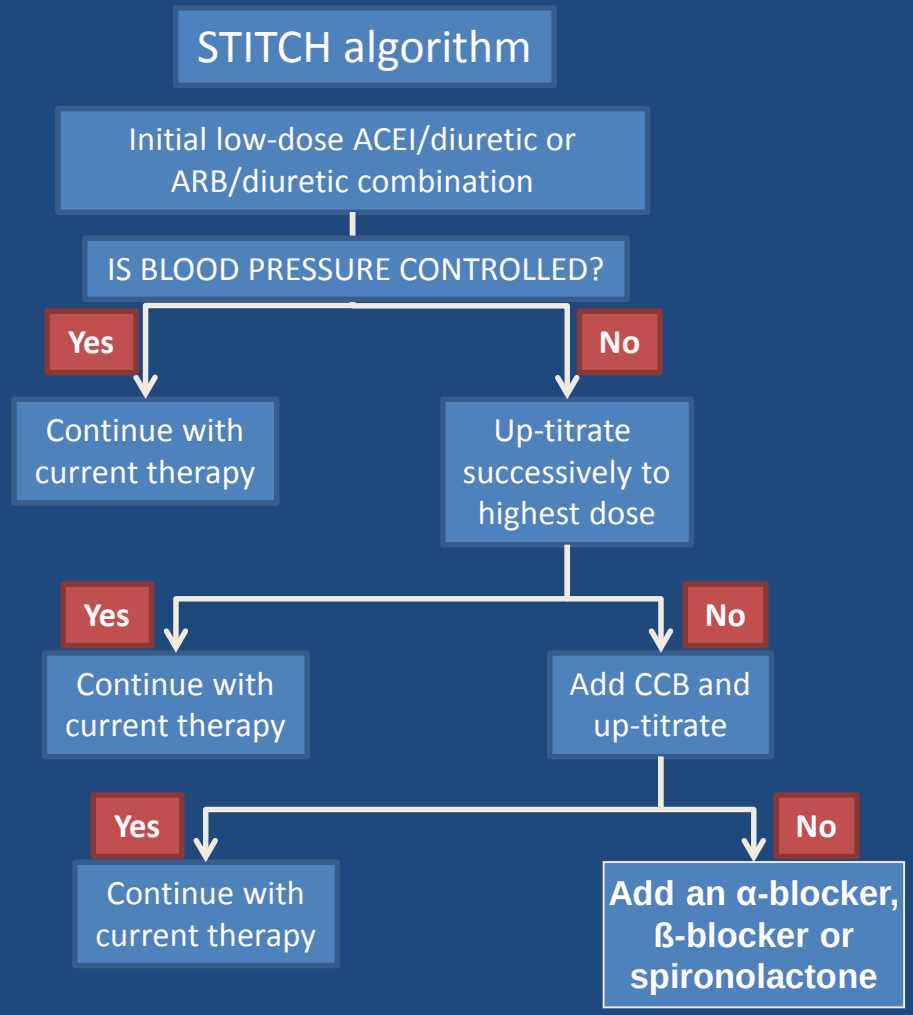
STITCH-Care Algorithm (Canada)

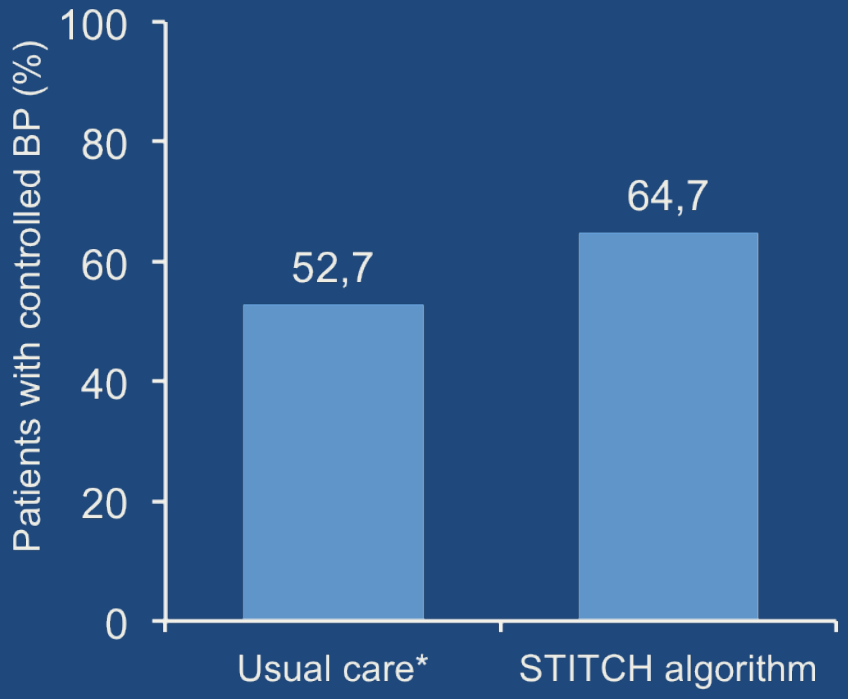


Achieving BP goal
Algorithm: 65% vs Usual Guideline driven GP care 53% (<0.02)

Feldman et al. Hypertension 2009;53:646–53

Concept 1: A treatment algorithm can achieve effective BP control in the general population

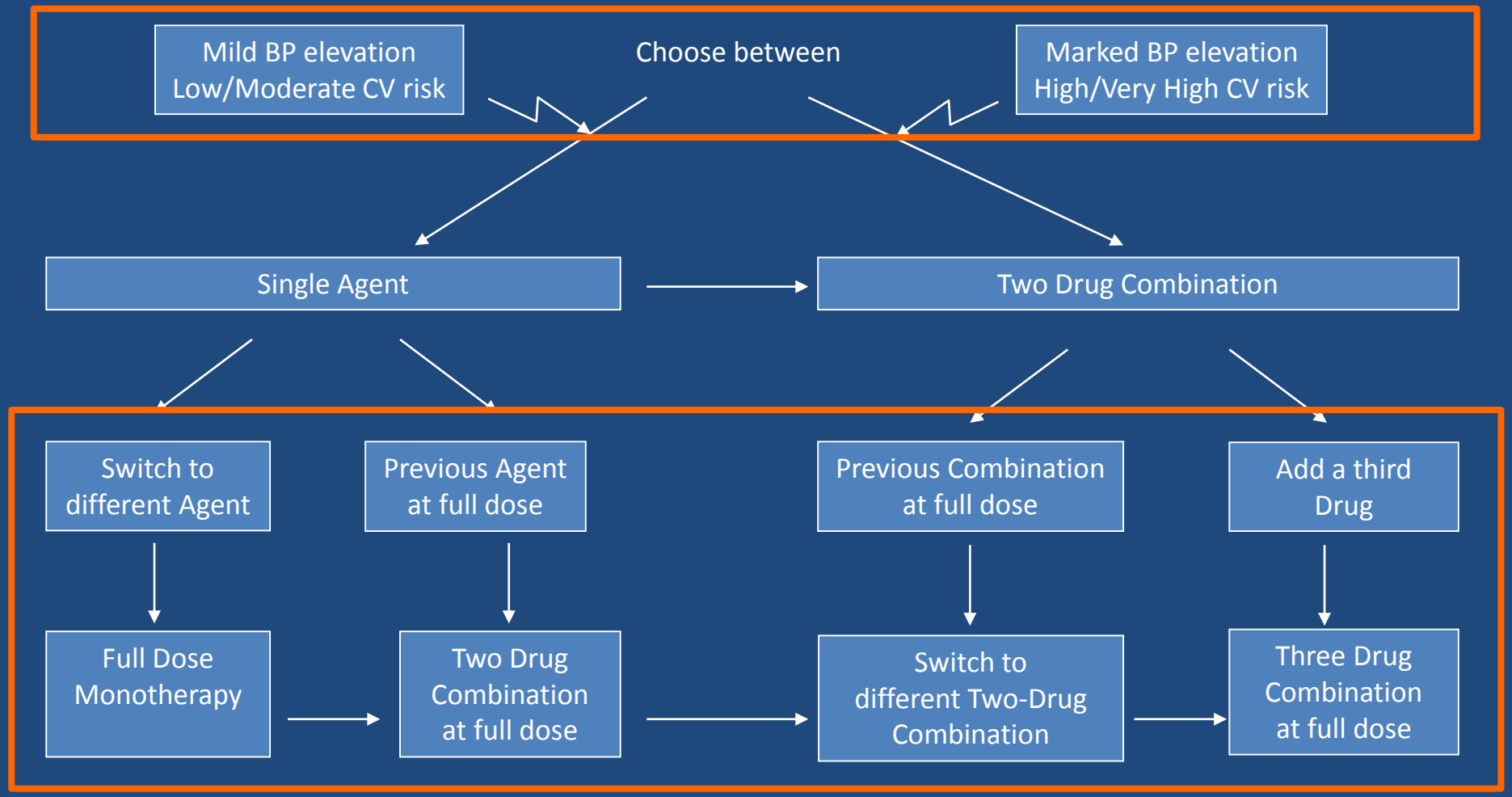




*Based on Canadian Hypertension Education Program (CHEP) guidelines

Adapted from Feldman et al. Hypertens 2009;53:646–53

Concept 2 Simplify Treatment by implementing use of combinations to achieve target BP



Mancia G, et al. Eur Heart J 2013 Jul;34(28):2159-219

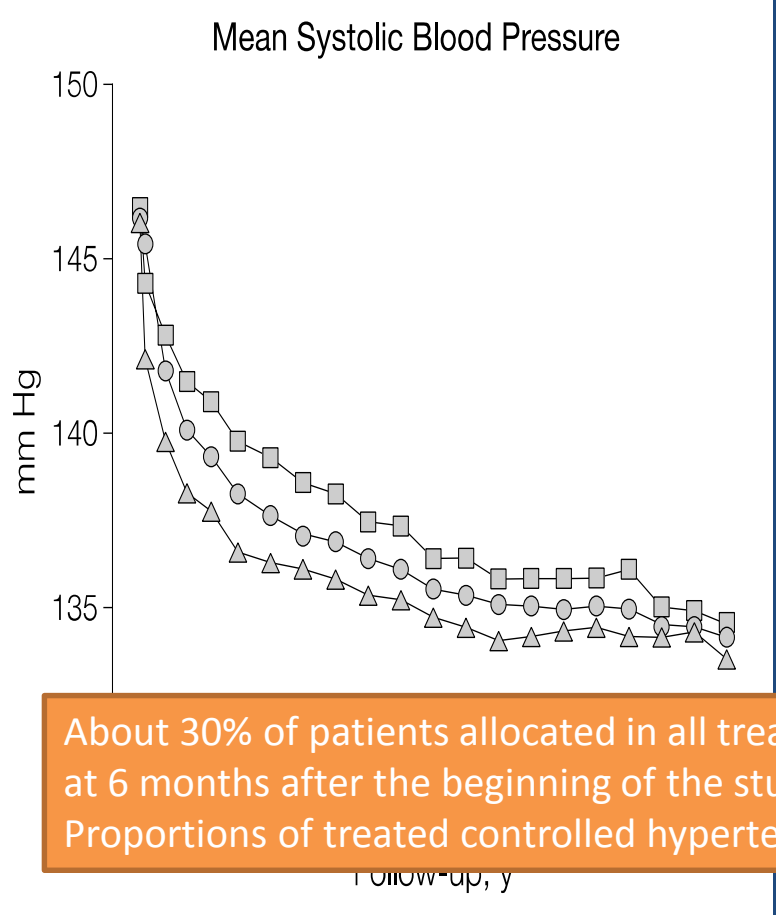
Treatment strategies and choice of drugs

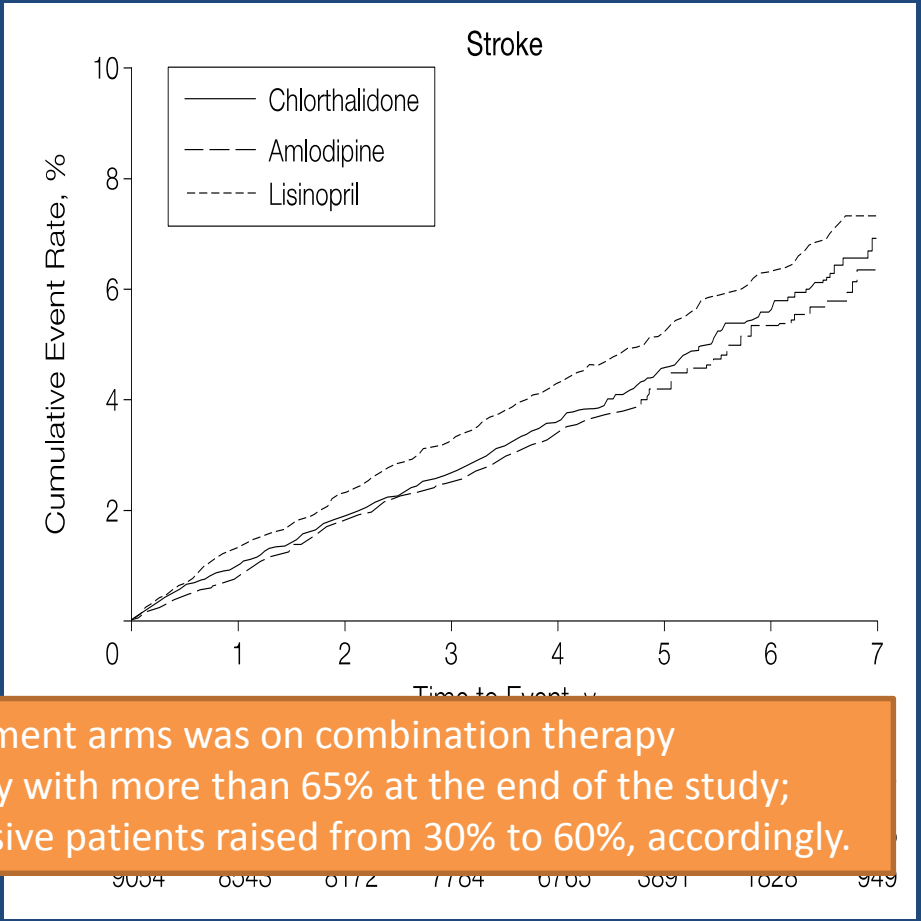
Recommendations	Class	Level
Diuretics (thiazides, chlorthalidone and indapamide), beta-blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor blockers are all suitable and recommended for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations with each other.	I	A
Some agents should be considered as the preferential choice in specific conditions be … typ …	IIa	C
Ini… pa…	IIb	C
The combination of two antagonists of the RAS is not recommended and should be discouraged.	III	A
Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable.	IIa	C
Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favoured, because reducing the number of daily pills improves adherence, which is low in patients with hypertension.	IIb	B

However, there are substantial differences among various classes of antihypertensive drugs

Mancia G, et al. Eur Heart J 2013 Jul;34(28):2159-219

BP reductions and Kaplan-Meier curves for a component of the Primary Endpoint (Fatal and non-fatal Stroke)

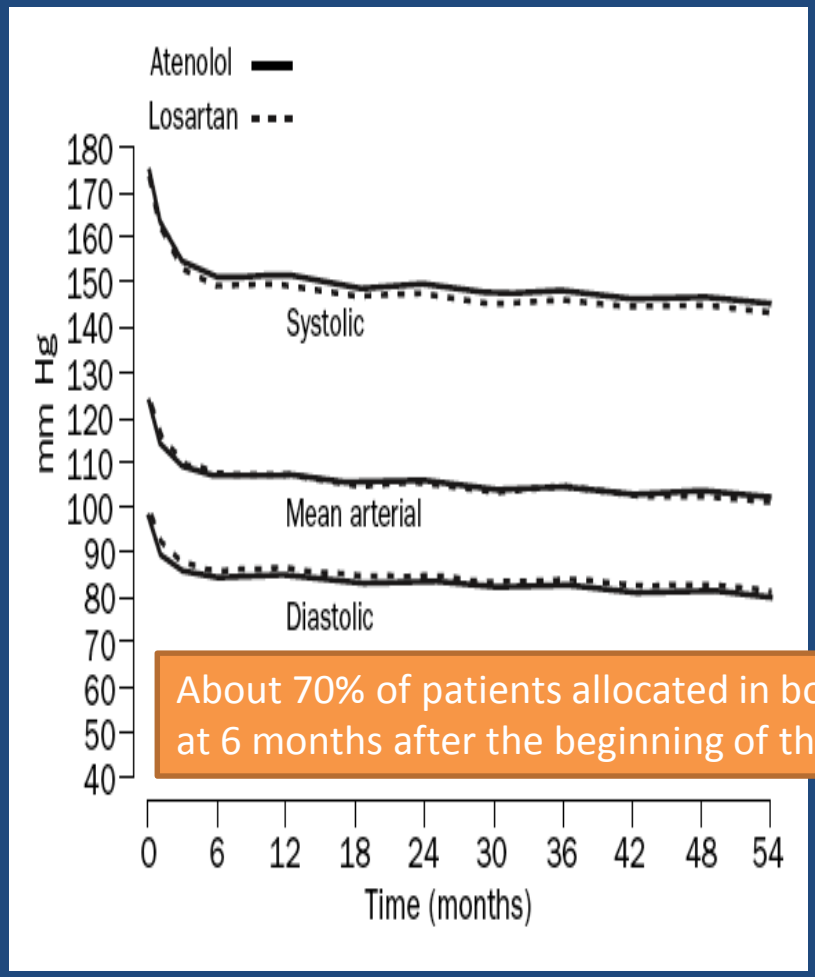


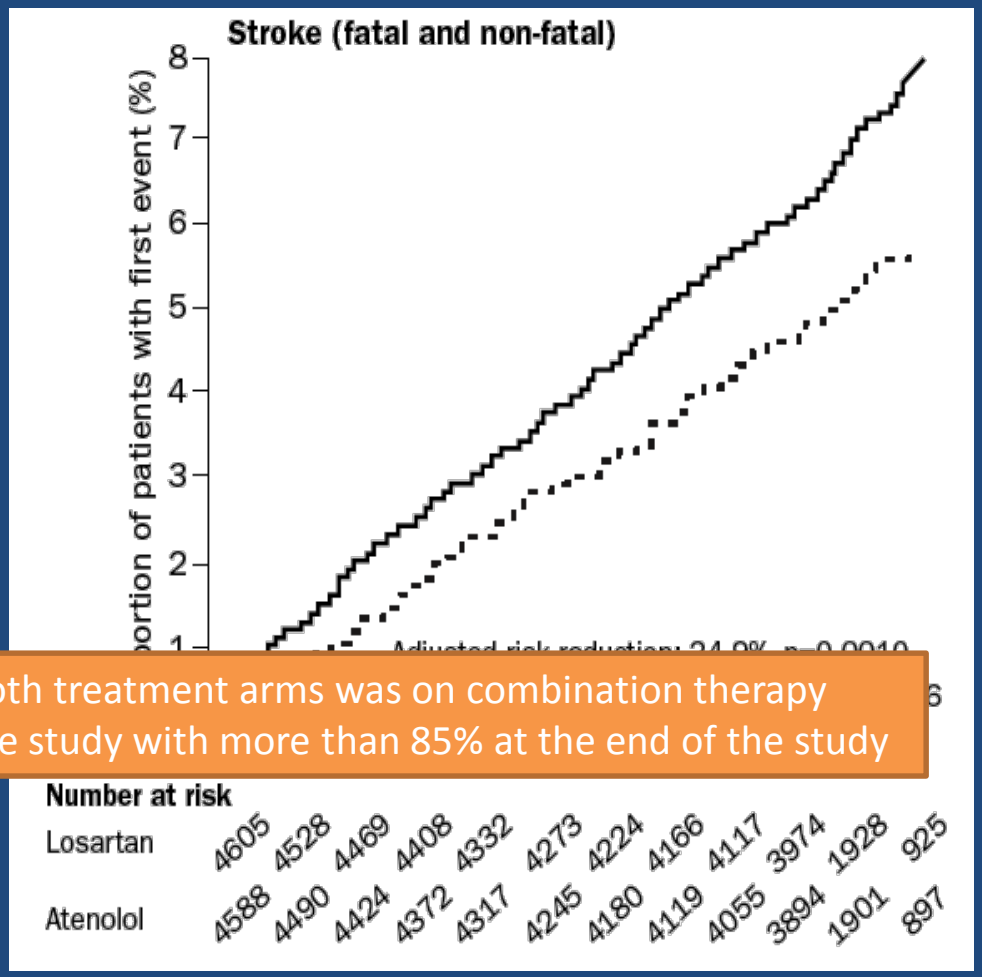


About 30% of patients allocated in all treatment arms was on combination therapy at 6 months after the beginning of the study with more than 65% at the end of the study; Proportions of treated controlled hypertensive patients raised from 30% to 60%, accordingly.

1. The ALLHAT Study Group. JAMA 2002;288;2981-2997
2. Cushman et al. J Clin Hypertens 2002;4:393-404

BP reductions and Kaplan-Meier curves for a component of the Primary Endpoint (Fatal and non-fatal Stroke)

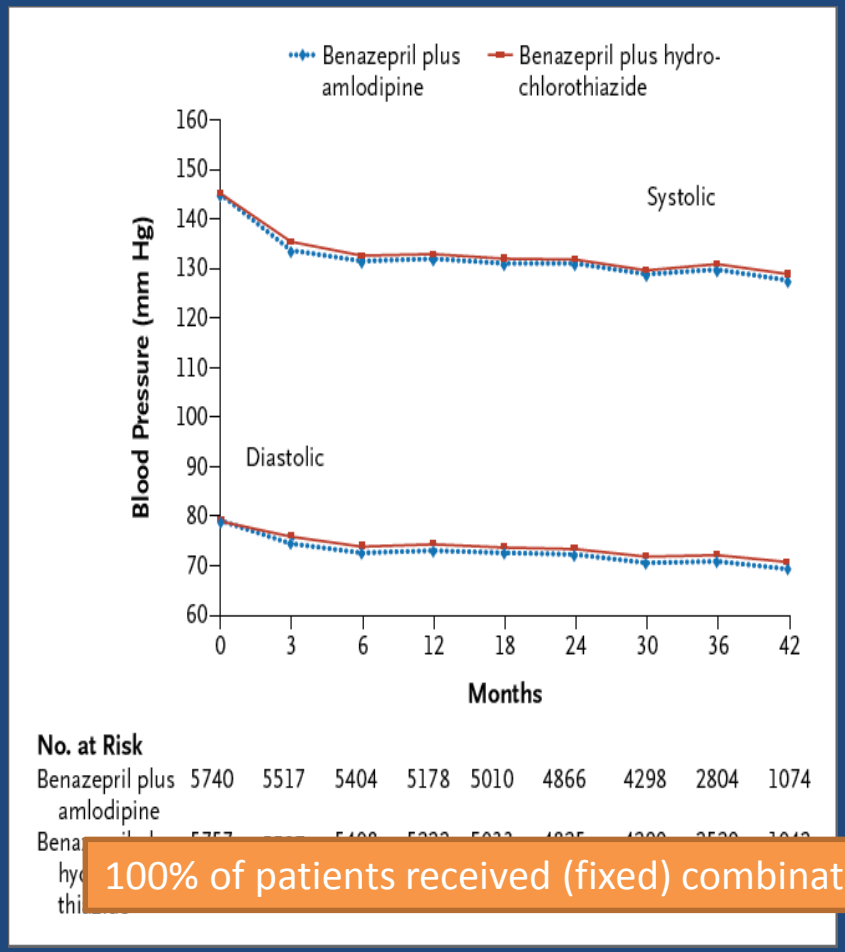


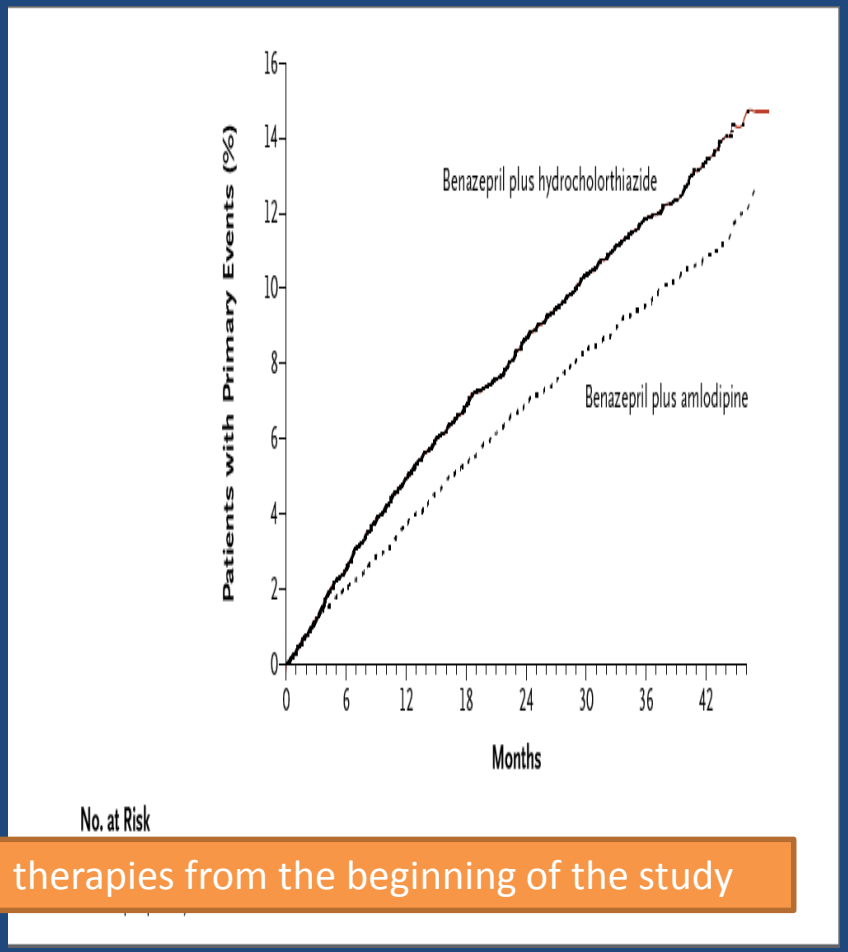


About 70% of patients allocated in both treatment arms was on combination therapy at 6 months after the beginning of the study with more than 85% at the end of the study

Dahlof B, et al. Lancet 2002;359:995-1003

BP reductions and Kaplan-Meier curves for the Primary Composite Endpoint (Stroke, CHD, CV mortality)





100% of patients received (fixed) combination therapies from the beginning of the study

Jamerson JA, et al. N Engl J Med 2008;359:2417-28

How to improve BP control in daily clinical practice of hypertension?

POSITION PAPER

Strategie per migliorare il controllo della pressione arteriosa in Italia: dalla stratificazione del rischio cardiovascolare globale alla terapia di combinazione

Documento di Indirizzo 2012 della Società Italiana dell'Ipertensione Arteriosa (SIIA)

Massimo Volpe[1], Ettore Ambrosioni[2], Claudio Borghi[2], Santina Cottone[3], Cesare Cuspidi[4], Nicola De Luca[5], Francesco Fallo[6], Claudio Ferri[7], Alberto Morganti[8], Maria Lorenza Muiesan[9], Riccardo Sarzani[10], Leonardo Sechi[11], Agostino Virdis[12], Giuliano Tocci[1], Enrico Agabiti-Rosei[13], Bruno Trimarco[6], Alessandro Filippi[14], Giuseppe Mancia[4]

Volpe M, et al. G Ital Cardiol (Rome) 2012 Dec;13(12):853-60
Volpe M, et al. Ipertensione Prev Cardiovasc 2012;19(4):187-196
Volpe M, et al. High Blood Press Cardiovasc Prev 2013 Mar;20(1):45-52

ARB-based hypertension treatment platform

- Using a single-pill therapy identified by a platform may help to improve adherence
- The platform outlines how the majority of patients with hypertension can be effectively treated in general practice with an ARB like OLM, combined with AML and/or HCTZ
- The platform identifies the correct therapy for patients with varying characteristics and needs
  - Based on clinical evidence, guidelines, best practice and clinical experience
- To improve adherence, the use of single-pill FDCs is recommended
  - For practical reasons the platform is based on OLM, which is available as monotherapy and in single-pill combinations with AML and/or HCTZ
  - OLM/AML/HCTZ is the only ARB-based triple combination with an add-on indication

ARB single-pill platform: Hypertensive patients with specific risk factors or subclinical organ damage

	Grade 1 SBP 140–159 or DBP 90–99	Grade 2 SBP 160–179 or DBP 100–109	Grade 3 SBP ≥180 or DBP ≥110
No risk factors	OLM 10–20 mg	OLM/AML 20/5 mg*	OLM/AML 20–40/10 mg*
		OLM/HCTZ 20/12.5 mg*	OLM/HCTZ 20–40/25 mg*
Dyslipidaemia, hyperuricaemia, obesity, or metabolic syndrome	OLM 10–20 mg	OLM/AML 20/5 mg*	OLM/AML 20–40/5–10 mg*
Fit elderly, <80 years old	OLM 10–20 mg if well tolerated	OLM/HCTZ 20/12.5 mg*	OLM/HCTZ 20–40/25 mg*
Frail elderly, >80 years old, SBP ≥160 mmHg	Consider OLM 10–20 mg	OLM/HCTZ 10–20/12.5 mg*	OLM/HCTZ 20–40/25 mg*
Atherosclerosis, arteriosclerosis, or PAD	Consider OLM 10–20 mg	OLM/AML 20–40/5 mg	OLM/AML 20–40/10 mg
LV hypertrophy	OLM 20–40 mg	OLM/HCTZ 20–40/12.5 mg*	OLM/HCTZ 20–40/25 mg*
Microalbuminuria/proteinuria (CKD stage ≤3)	OLM 20–40 mg	OLM/AML 40/5 mg	OLM/AML 40/10 mg
Diabetes	OLM 20–40 mg	OLM/AML 40/5 mg*	OLM/AML 40/10 mg*

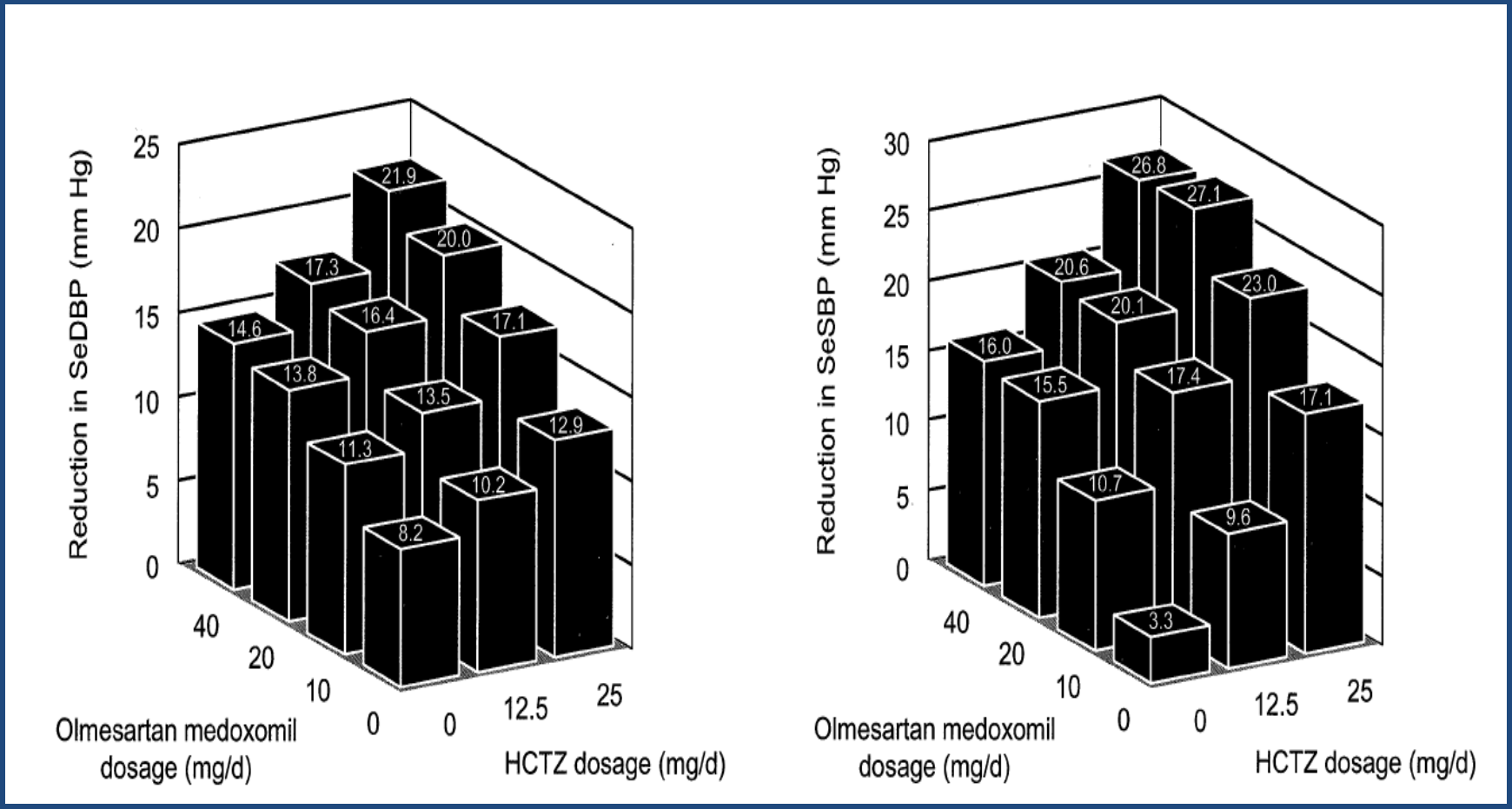
Volpe M, et al. High Blood Press Cardiovasc Prev 2014;21(2):137-147

ARB single-pill platform: Hypertensive patients who have overt organ damage

	Grade 1 SBP 140–159 or DBP 90–99	Grade 2 SBP 160–179 or DBP 100–109	Grade 3 SBP ≥180 or DBP ≥110
Atrial fibrillation	OLM 20–40 mg	OLM/HCTZ 20–40/12.5 mg	OLM/HCTZ 20–40/25 mg
Nephropathy (CKD stage >3) eGFR <30 mL/min/1.73m^2	OLM 20–40 mg	OLM/AML 40/5 mg	OLM/AML 40/10 mg
Coronary artery disease	OLM 10–20 mg	OLM/HCTZ 20–40/12.5 mg*	OLM/HCTZ 40/25 mg*
Previous stroke or transient ischaemic attack	OLM 10–20 mg	OLM/AML 20–40/5 mg*	OLM/AML 20–40/10 mg*
Heart failure with reduced EF	OLM/HCTZ 10–20/12.5 mg	OLM/HCTZ 20–40/12.5 mg*	OLM/HCTZ 20–40/25 mg*

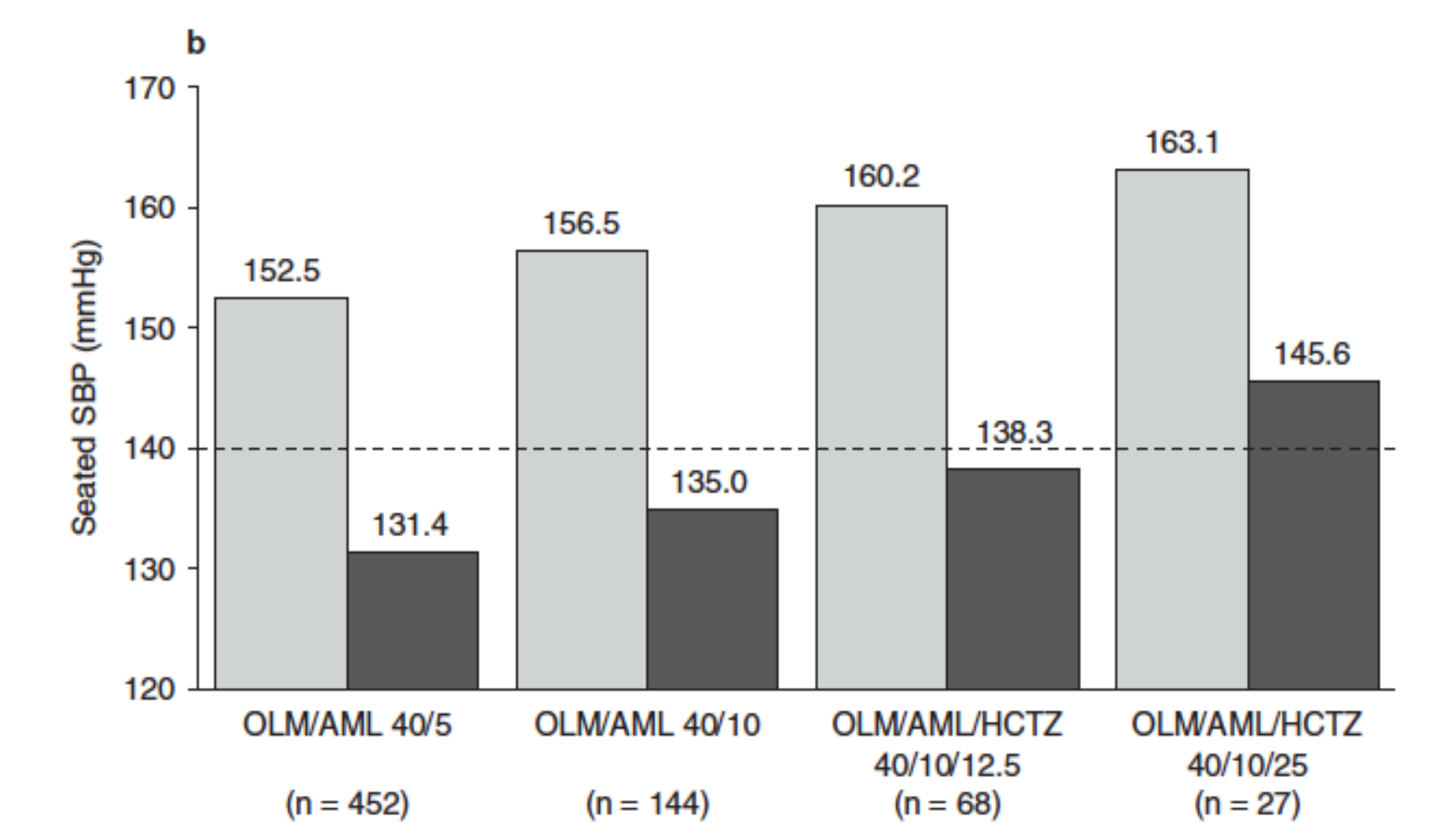
Volpe M, et al. High Blood Press Cardiovasc Prev 2014;21(2):137-147

Reduction (model fitted) in seated diastolic blood pressure (SeDBP) for 12 groups in the factorial design by olmesartan medoxomil and hydrochlorothiazide (HCTZ) dosage.



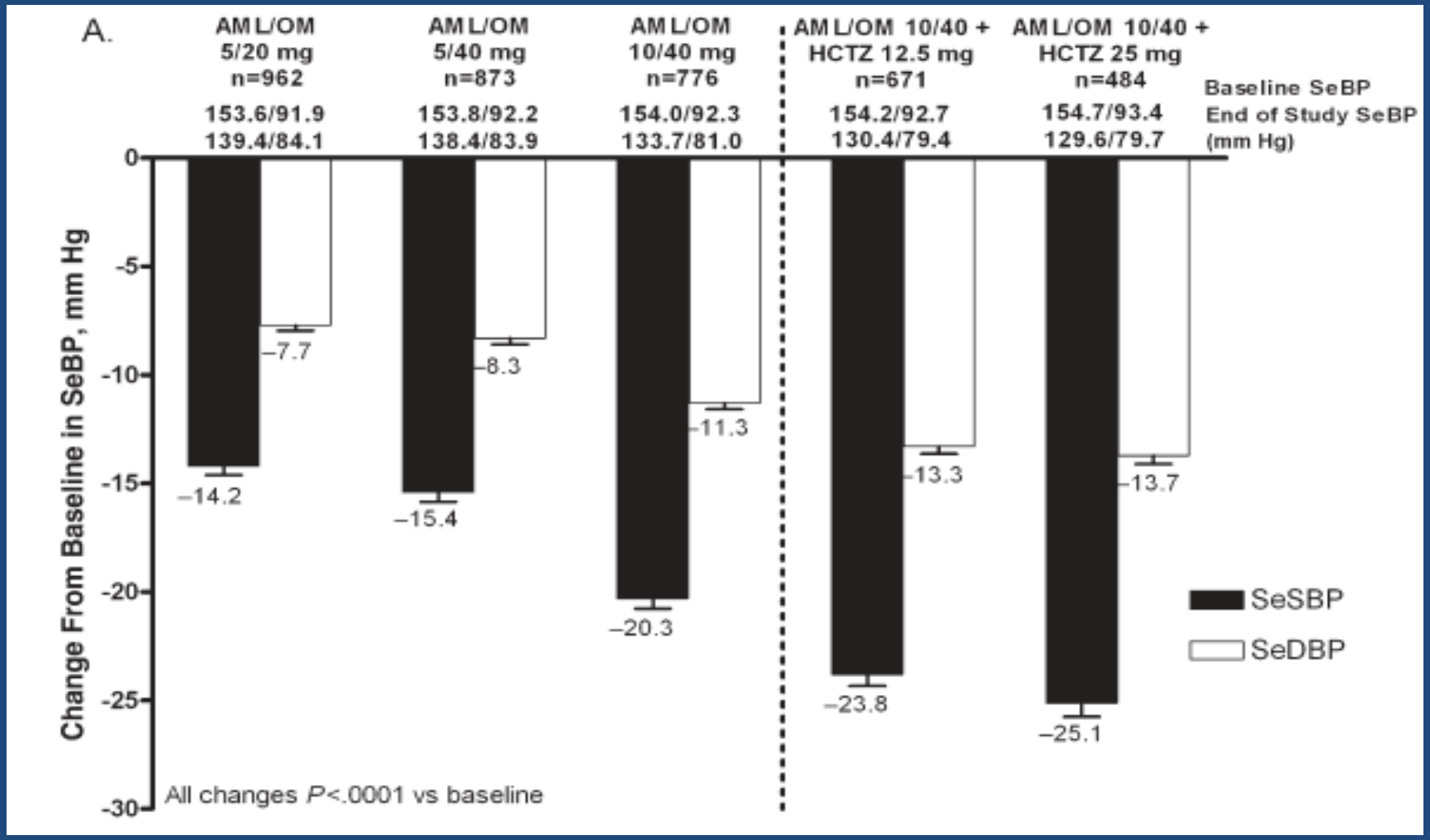
Chrysant SG, et al. Am J Hypertens 2004;17:252–59

Mean seated (**b**) systolic (SBP) blood pressure after 8 weeks of open-label treatment with amlodipine (AML) 5mg and at the end of the open-label regimen (52 weeks) or early withdrawal



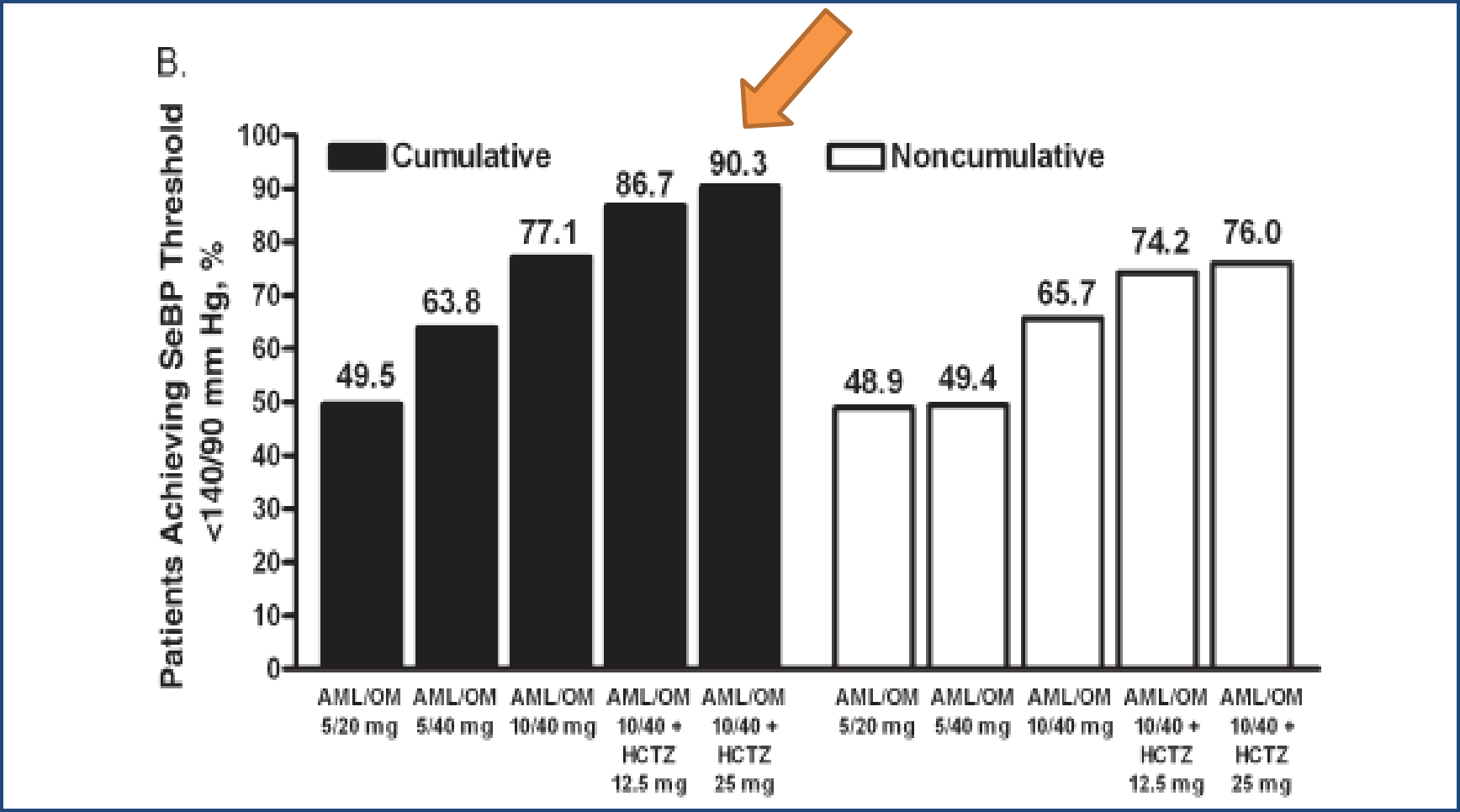
Volpe M, et al. Clin Drug Invest 2009;29(6):381-391

Change from baseline in seated cuff systolic (SeSBP) and diastolic (SeDBP) blood pressure levels with different combination therapies based on olmesartan/amlodipine/HCTZ



Weir et al. J Clin Hypertens 2011;13:404–412

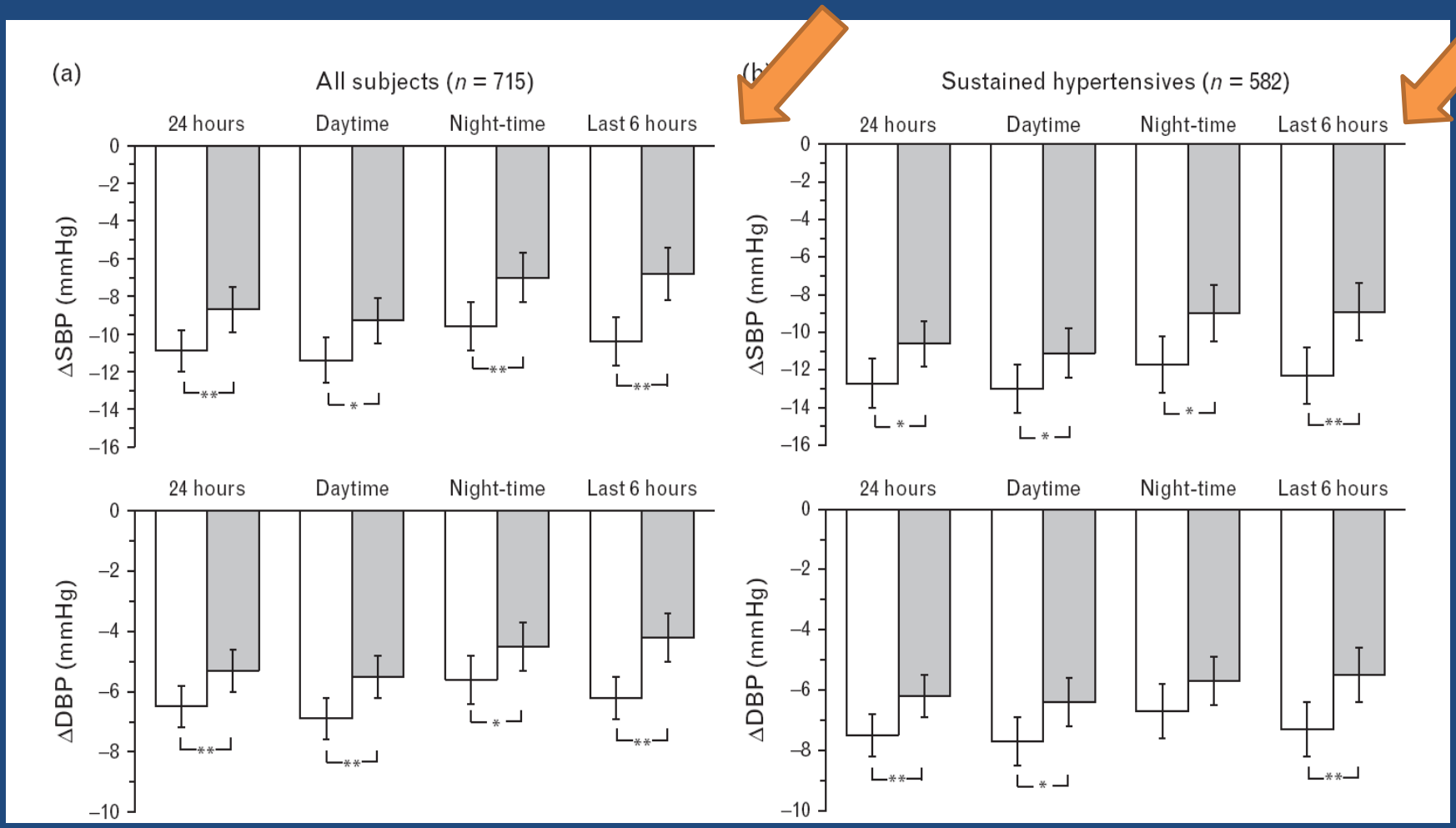
Proportions of patients achieving Seated Blood Pressure (SeBP threshold of <140 / 90 mmHg by titration dose with different combination therapies based on olmesartan/amlodipine/HCTZ



Weir et al. J Clin Hypertens 2011;13:404–412

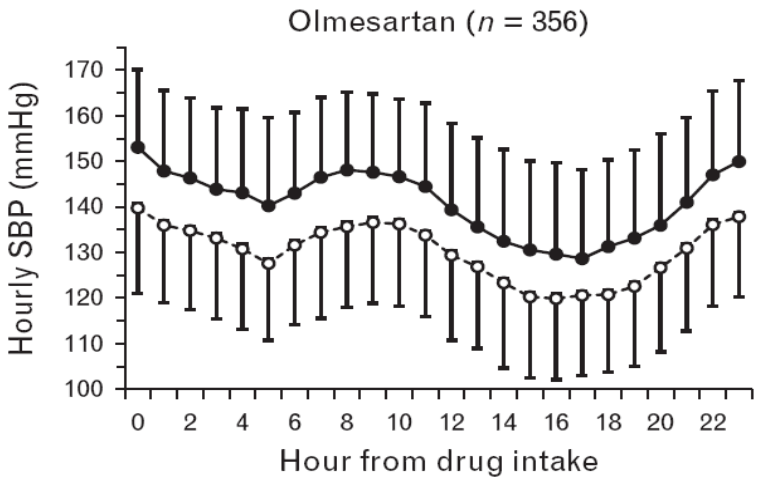
ESPORT Trial

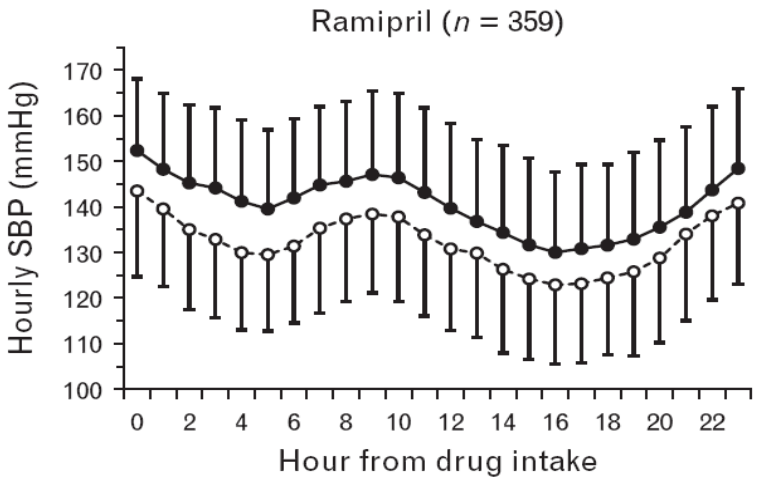
Baseline-adjusted 24 h, daytime, night-time and last 6 h SBP and DBP mean changes (95% confidence intervals) after 12 weeks of double-blind treatment with olmesartan 10–40mg (open bars) and ramipril 2.5-10mg (gray bars). Data are shown for the whole population (n=715, panel a) and for sustained hypertensive patients (n=582, panel b).

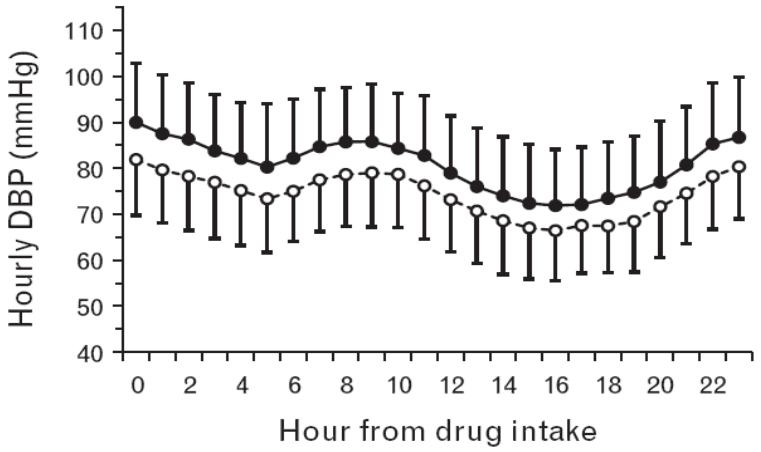


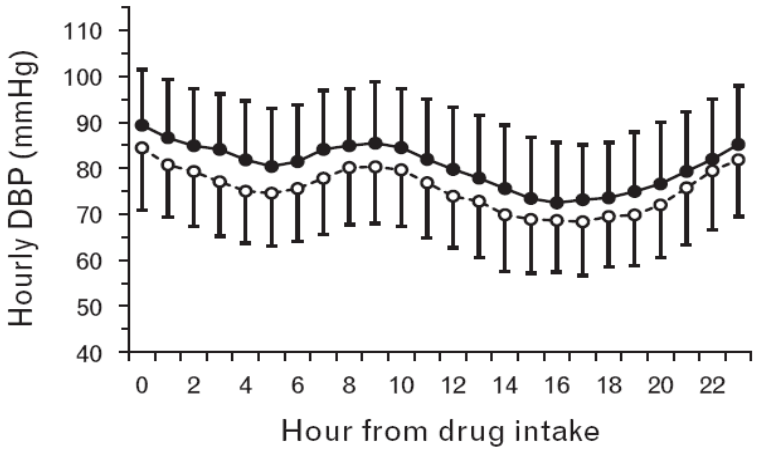
Omboni S, Volpe M, et al. J Hypertens 2012 Jul;30(7):1468-77

Average (SD) hourly SBP and DBP values at baseline (continuous line) and at the end of the 12-week double-blind treatment (dashed lines) in patients treated with olmesartan 10–40mg (n=356) or ramipril 2.5–10mg (n=359)









Omboni S, Volpe M, et al. J Hypertens 2012 Jul;30(7):1468-77

Nuova *Mission*
della Società Italiana dell'Ipertensione Arteriosa (SIIA)

Obiettivo SIIA

70%

Entro il 2015

Volpe M. High Blood Press Cardiovasc Prev 2012;19(1):1-3

Key Points of the Strategy

1. **Analysis of New Large Databases** ("street BP", GP database, European networks)

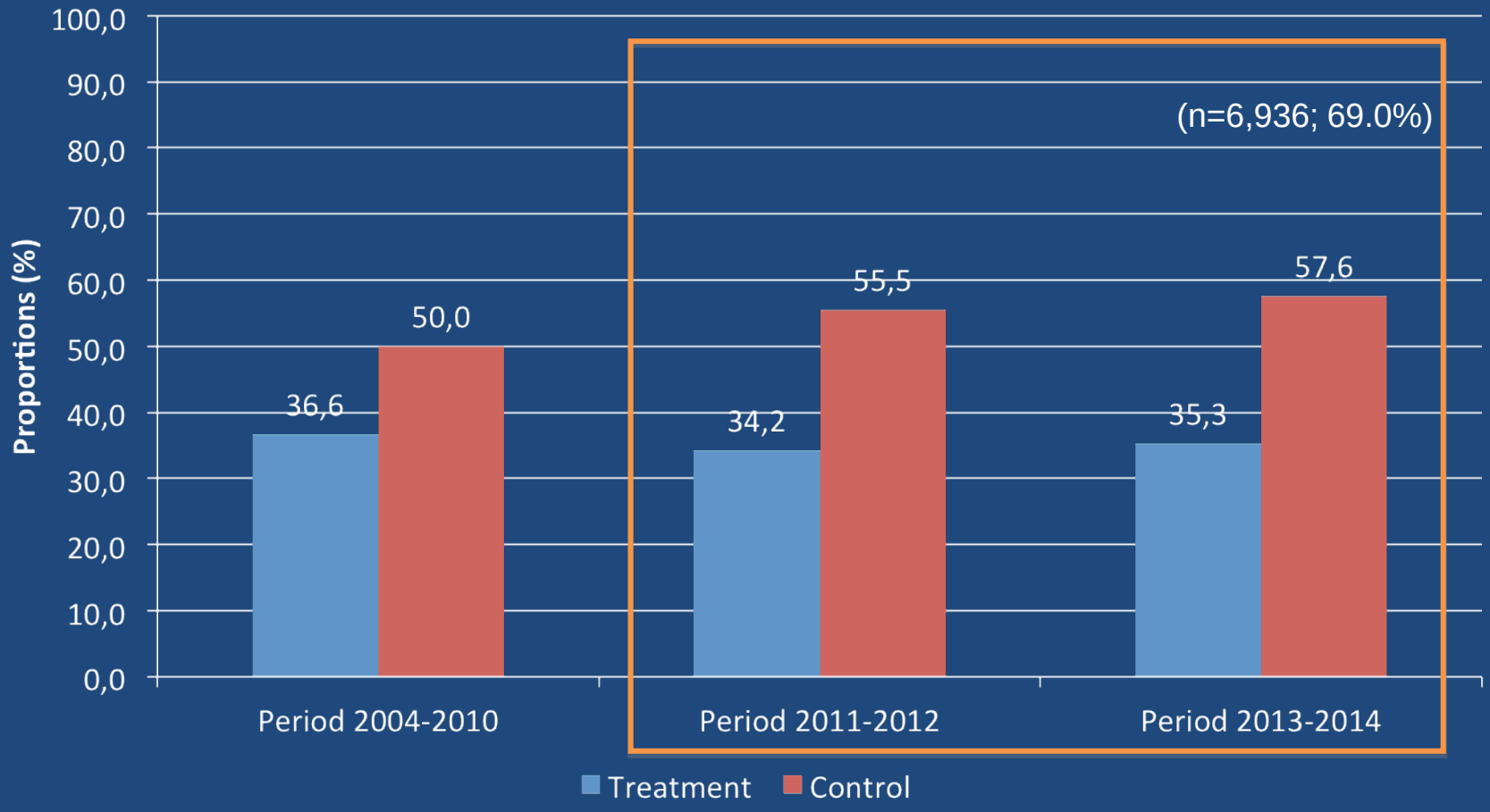
2. Implementation of Home BP Measurements (partnership with patients)

3. Simplification of Therapy (single pill combination)

4. Network of Italian Hypertension Centers

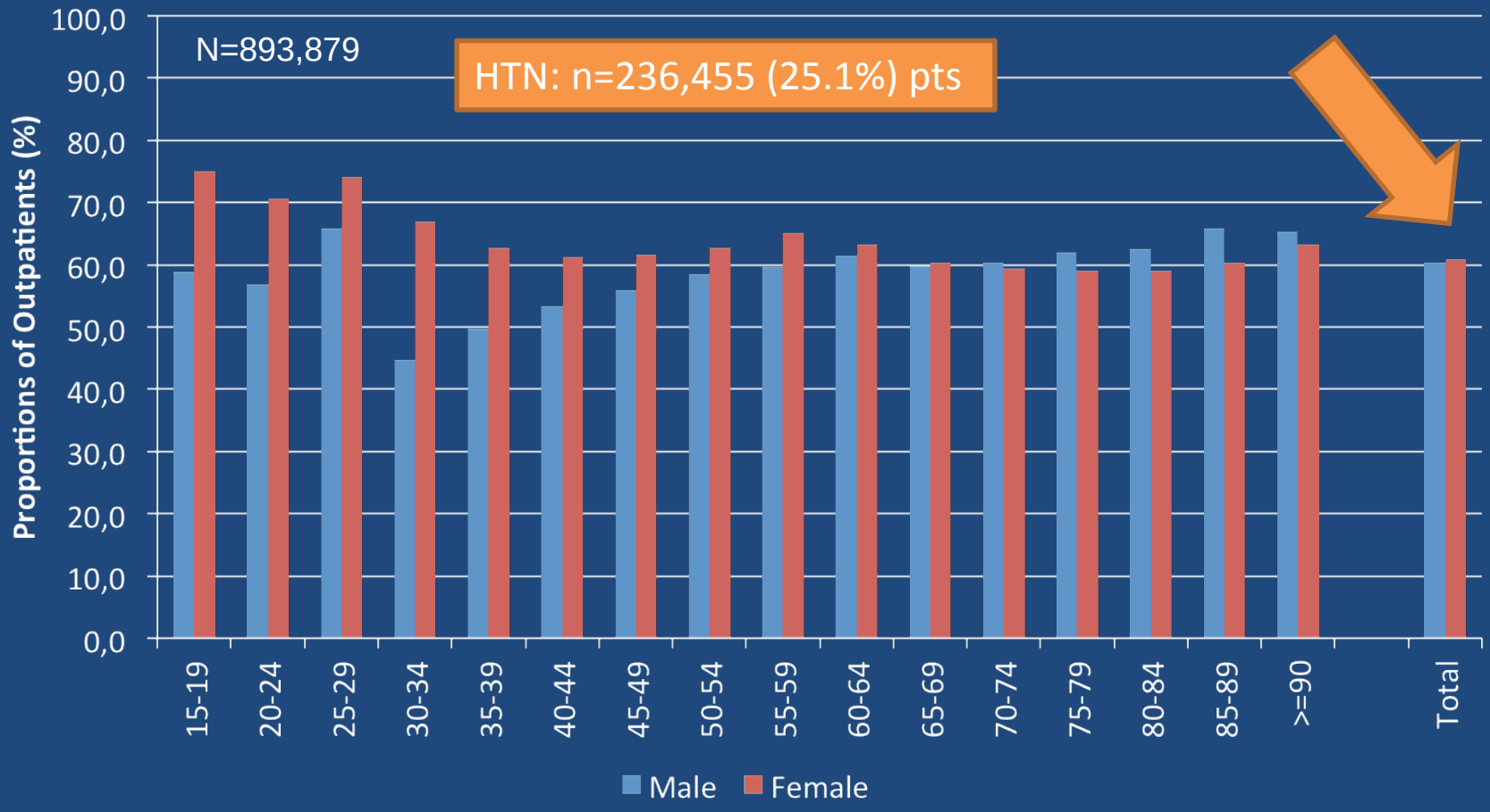
Volpe M, et al. G Ital Cardiol (Rome) 2012 Dec;13(12):853-60
Ipertensione Prev Cardiovasc 2013; *in press*
High Blood Press Cardiovasc Prev 2013 Mar 28. [Epub ahead of print]

World Hypertension Day in Italy: HTN Treatment and Control in 3 different time periods



Tocci G, Borghi C, Parati G, Volpe M, et al. J Clin Hypertens 2015; *in press*

Analysis from large database of GPs (year 2013): Control* of Hypertension according to Gender Groups



* Control rate was calculated among those HT outpatients who have their BP measures

Tocci G, Borghi C, Volpe M, et al. Manuscript in preparation 2015

Conclusive Remarks

- Hypertension still affects more than 25% of adult Italian individuals, with an approximately 60% rate of awareness among hypertensive patients.

- Two independent *ad interim* analyses, which covered a time period until 2013-2014, reported a marked improvement in average BP control rate, which raised from 30% to about 58%.

- This improvement in overall BP control will lead to a reduced incidence of stroke, CHD, and CHF which is difficult to estimate at this time, but will certainly involved several thousand individuals.

Tocci G, Borghi C, Parati G, Volpe M, et al. J Clin Hypertens 2015; *in press*

SIIA Objective 70%

- The Healthcare and Societal benefits of an improved control of hypertension in our Country, as outlined in the Objective of the Italian Society of Hypertension (SIIA), will represent a major progress in the control of the disease and will have significant implications for the Health and Economic burden of hypertension in Italy.

What's next?

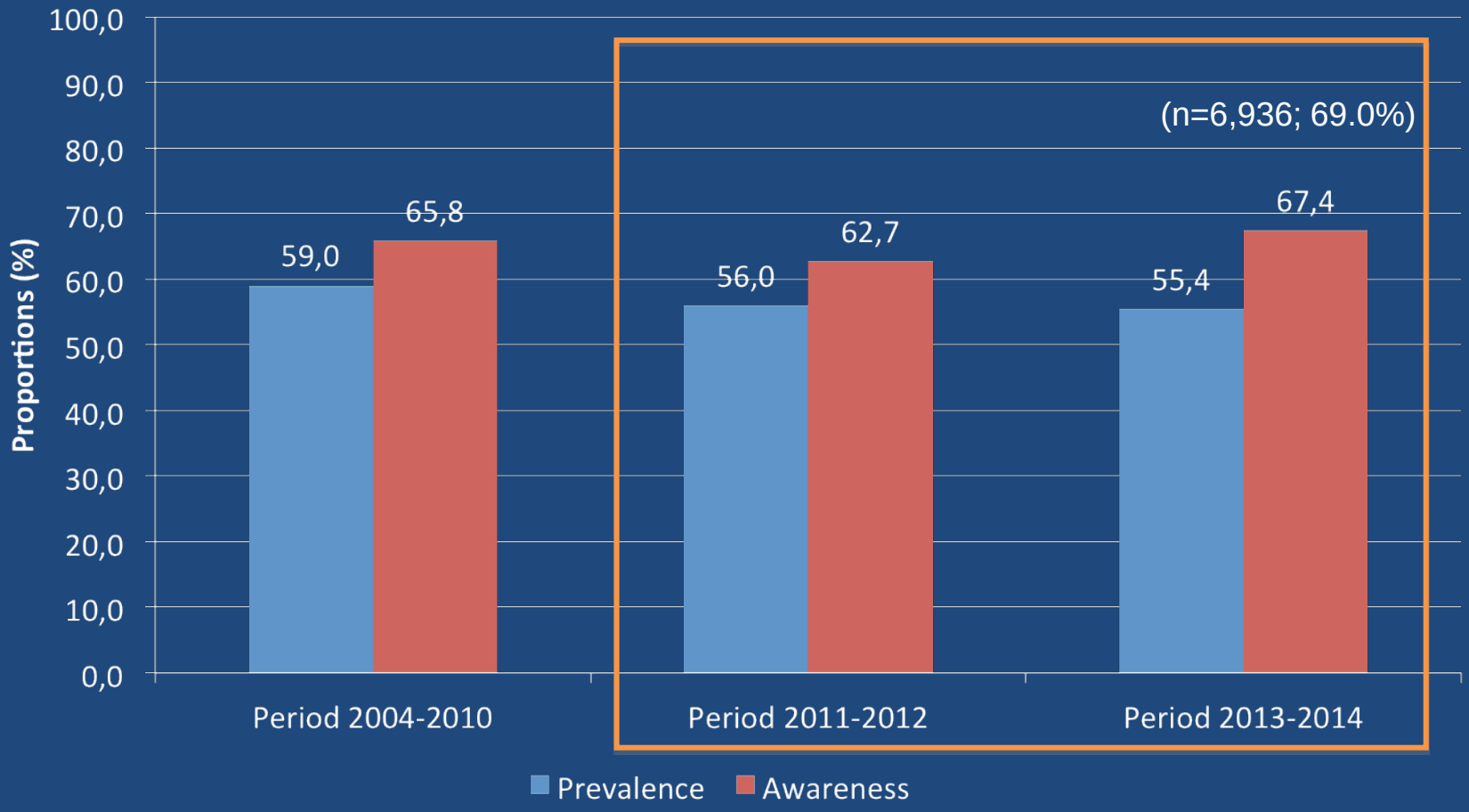
- Our generation of physicians has a concrete chance to control about 100% of hypertensive patients and to lead towards a major reduction in cardiovascular disease burden.

- International collaborations and networks, aiming at this goal also through a novel approach to practical recommendations, are required to achieve this ambitious healthcare target.

Thank you for Your Attention!

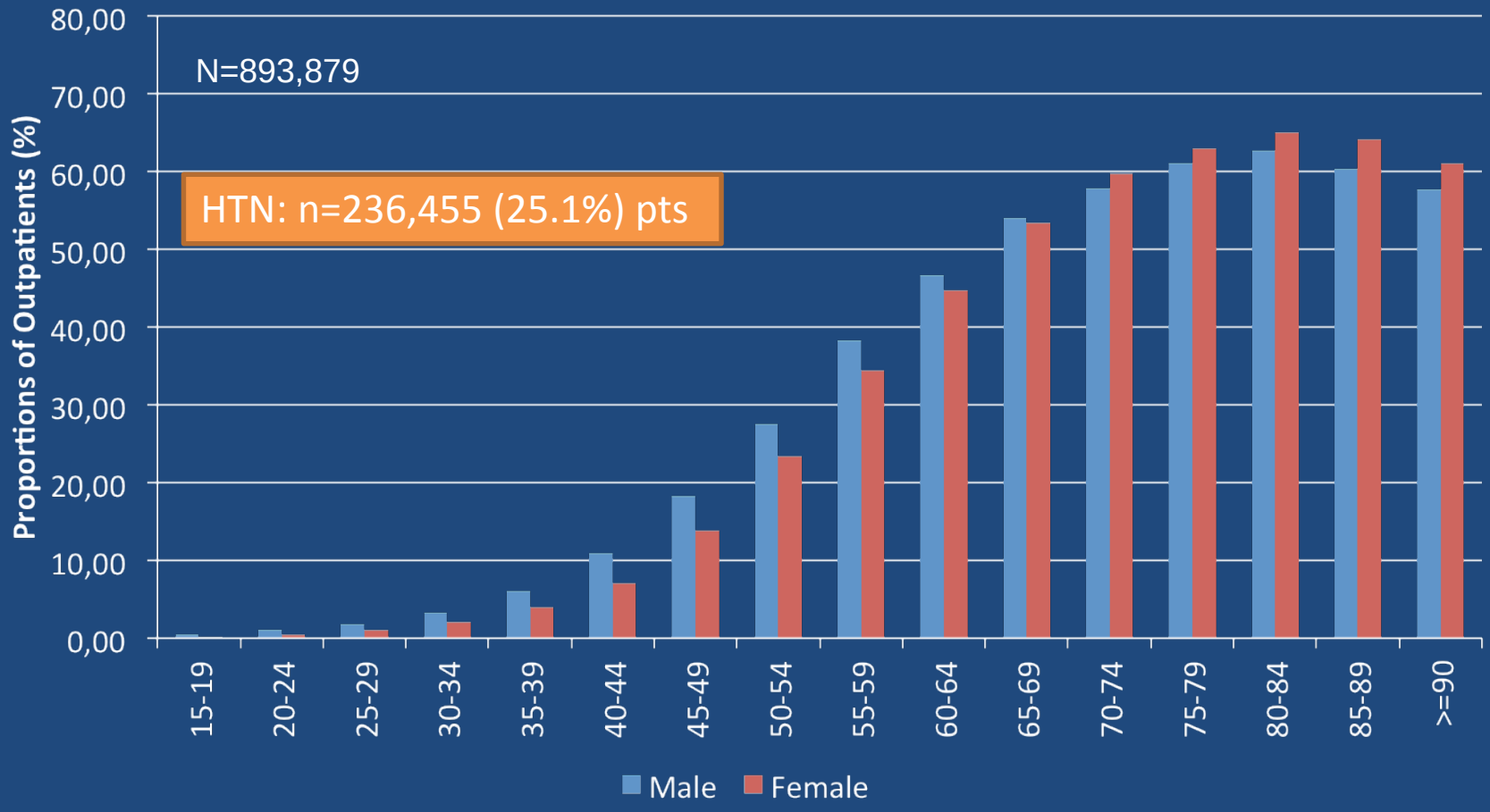
E: massimo.volpe@uniroma1.it

World Hypertension Day in Italy: HTN Prevalence and Awareness in 3 different time periods



Tocci G, Borghi C, Parati G, Volpe M, et al. J Clin Hypertens 2015; *in press*

Analysis from large database of GPs (year 2013): Prevalence of Hypertension according to Gender Groups



Tocci G, Borghi C, Volpe M, et al. Manuscript in preparation 2015

ORIGINAL RESEARCH | Annals of Internal Medicine

Burden of Changes in Pill Appearance for Patients Receiving Generic Cardiovascular Medications After Myocardial Infarction

Cohort and Nested Case–Control Studies

- To determine whether nonpersistent use of generic drugs among patients with CVD after myocardial infarction (MI) is associated with inconsistent appearance of their medications

RESULTS:

- The odds of nonpersistence in case patients increased by 34% after a change in pill color and 66% after a change in pill shape

Table 3. Association Between Nonpersistence and Color/Shape Discordance in Medications After MI

Change	Discordance Among Case Group (n = 4573), n (%)	Discordance Among Control Group (n = 19 881), n (%)	OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR for Pharmacy Change (95% CI)†	Adjusted OR for Use of a Mail-Order Pharmacy (95% CI)‡
Color	177 (3.9)	587 (3.0)	1.34 (1.13–1.59)	1.34 (1.12–1.59)	1.10 (0.91–1.32)	1.16 (0.97–1.39)
Shape	242 (5.3)	644 (3.2)	1.67 (1.43–1.95)	1.66 (1.43–1.94)	1.41 (1.19–1.66)	1.38 (1.18–1.62)
Color or shape	309 (6.8)	922 (4.6)	1.50 (1.31–1.71)	1.49 (1.30–1.71)	1.25 (1.08–1.45)	1.25 (1.09–1.44)
Color and shape	110 (2.4)	309 (1.6)	1.58 (1.27–1.98)	1.58 (1.27–1.98)	1.32 (1.05–1.66)	1.37 (1.09–1.72)

CONCLUSION:

Variation in the appearance of generic pills is associated with non-persistent use of these essential drugs after MI among patients with cardiovascular disease.

Addressing poor adherence: Reducing pill burden

- ARB
- CCB
- Diuretic

Example three-pill combinations

Monotherapies

OR

- ARB/CCB/Diuretic

Single-pill fixed-dose combination

How can we improve drug adherence?

Practical aspects

1. To detect

- Talk about non-compliance (increase awareness of the problem)
- Monitor the treatment whenever possible
- Identify and contact patients who are not showing up to consultations
- Focus on patients in whom therapeutic goals are not reached

How can we improve drug adherence?

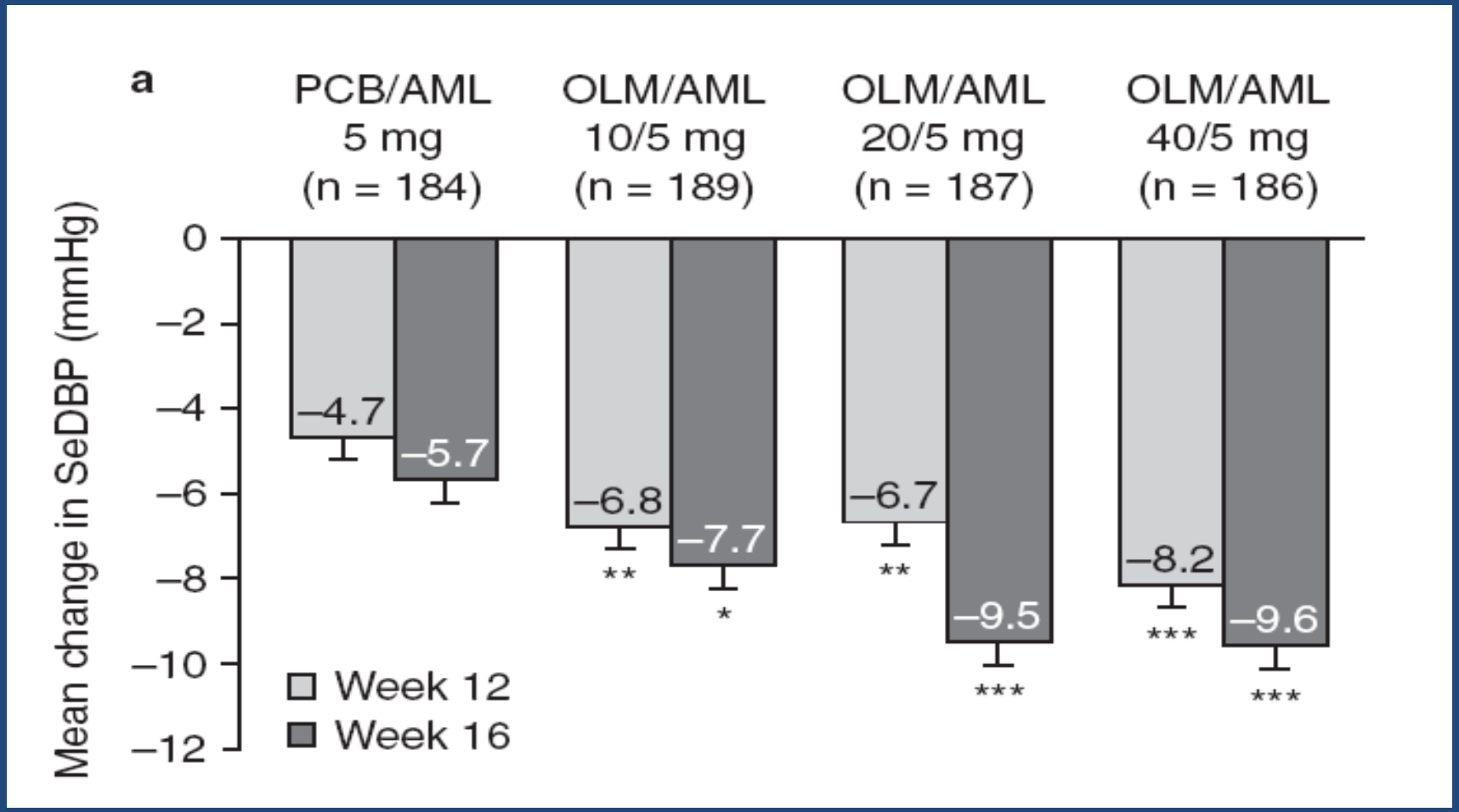
2. To prevent

- Give convenient appointments
- Simplify and adapt the treatment
- Give individualised instructions
- Promote patient’s collaboration with treatment

How can we improve drug adherence?

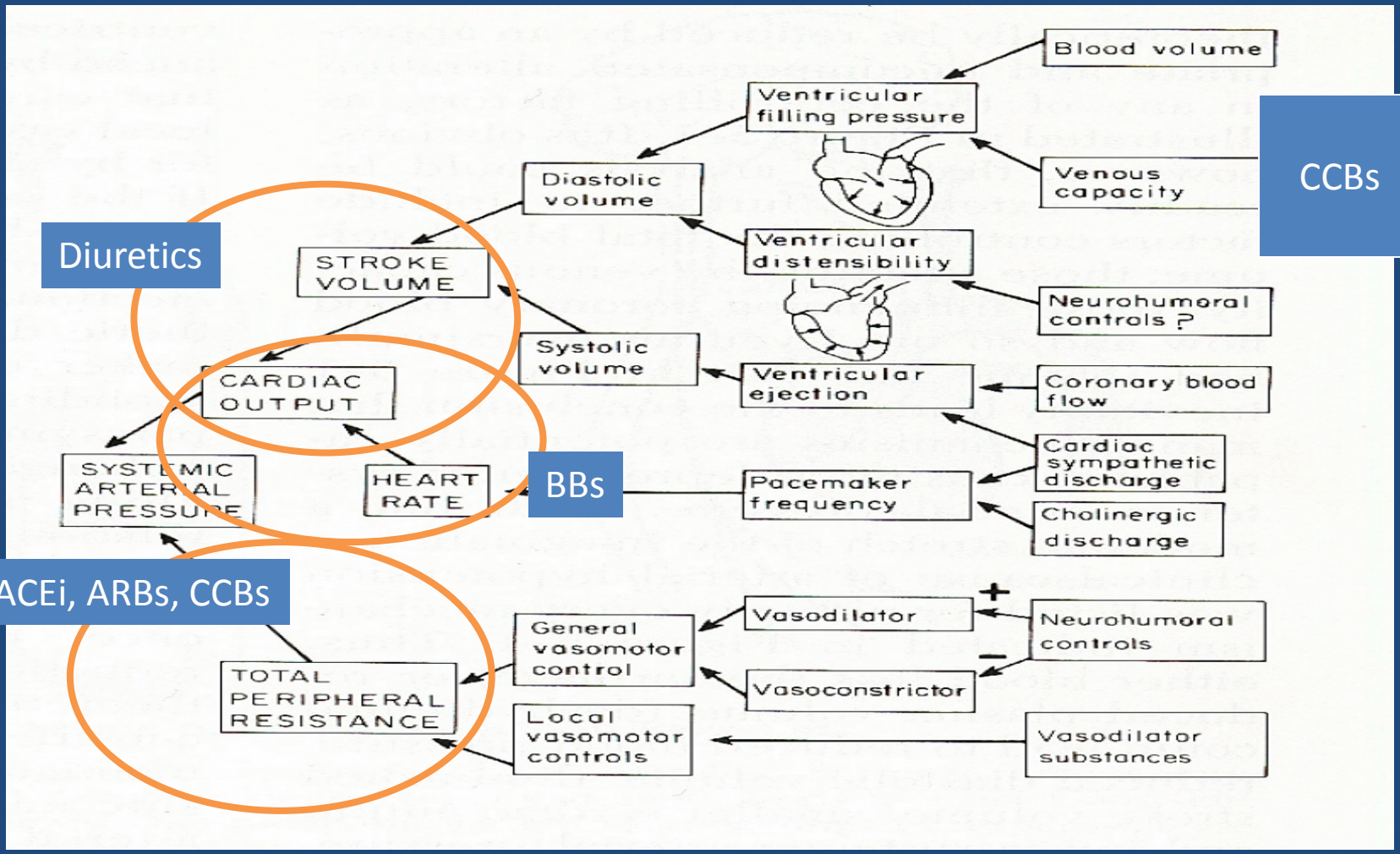
3. To maintain or to improve
    - Supervise the treatment
    - Couple drug taking to daily activities
    - Provide feedback on treatment to the patient
    - Positively reinforce adherence
    - Involve a family member or another partner

Mean change in seated Systolic BP (SeSBP) in essential grade 1-2 hypertensive patients with low-to-moderate CV risk profile

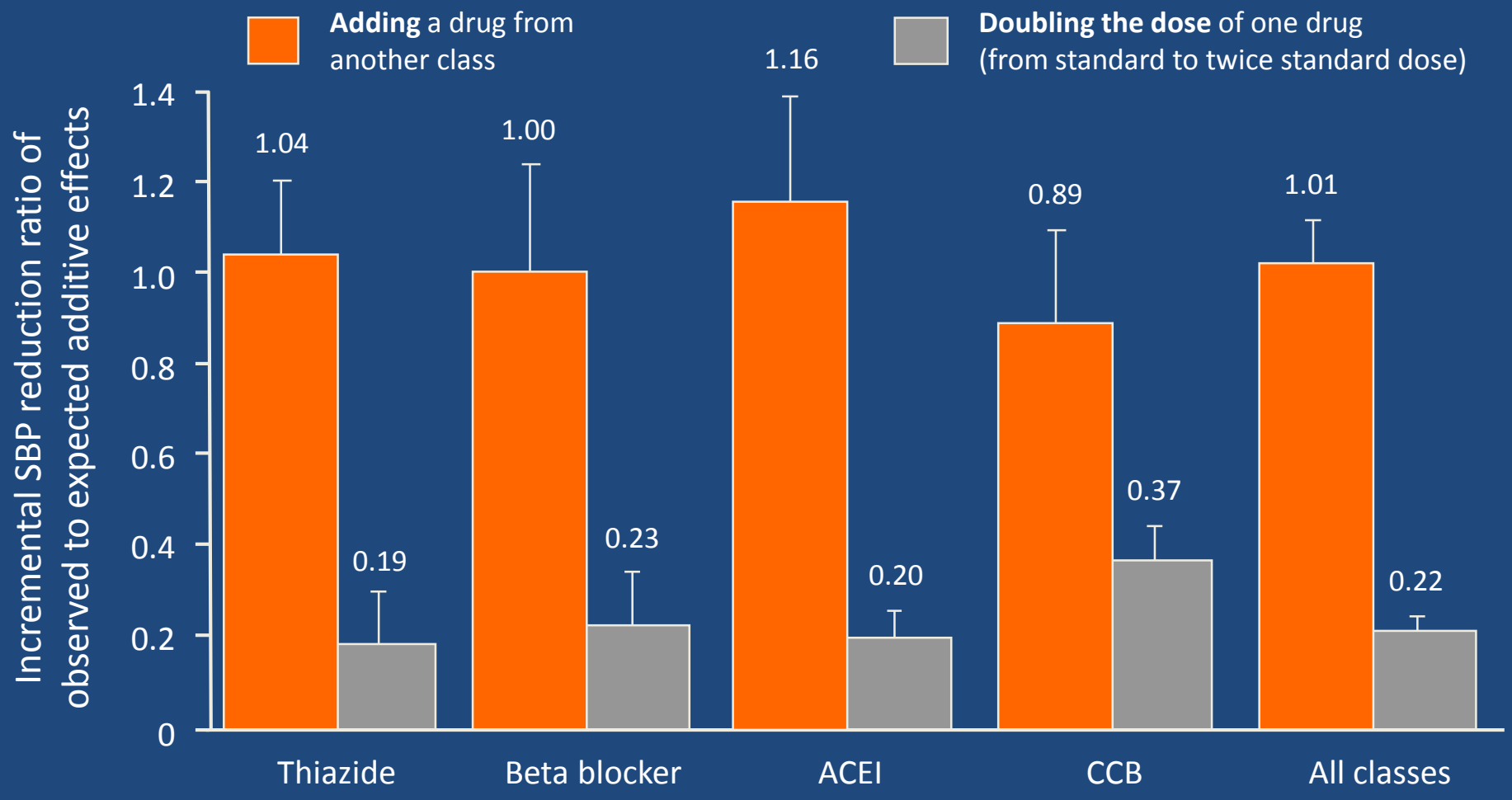


Volpe M, et al. Clin Drug Invest 2009;29(1):11–25

Factors Regulating BP:Complexity and Integration Support the Use of Combination Therapy



Rationale for combination therapy: two drugs are more effective than one drug

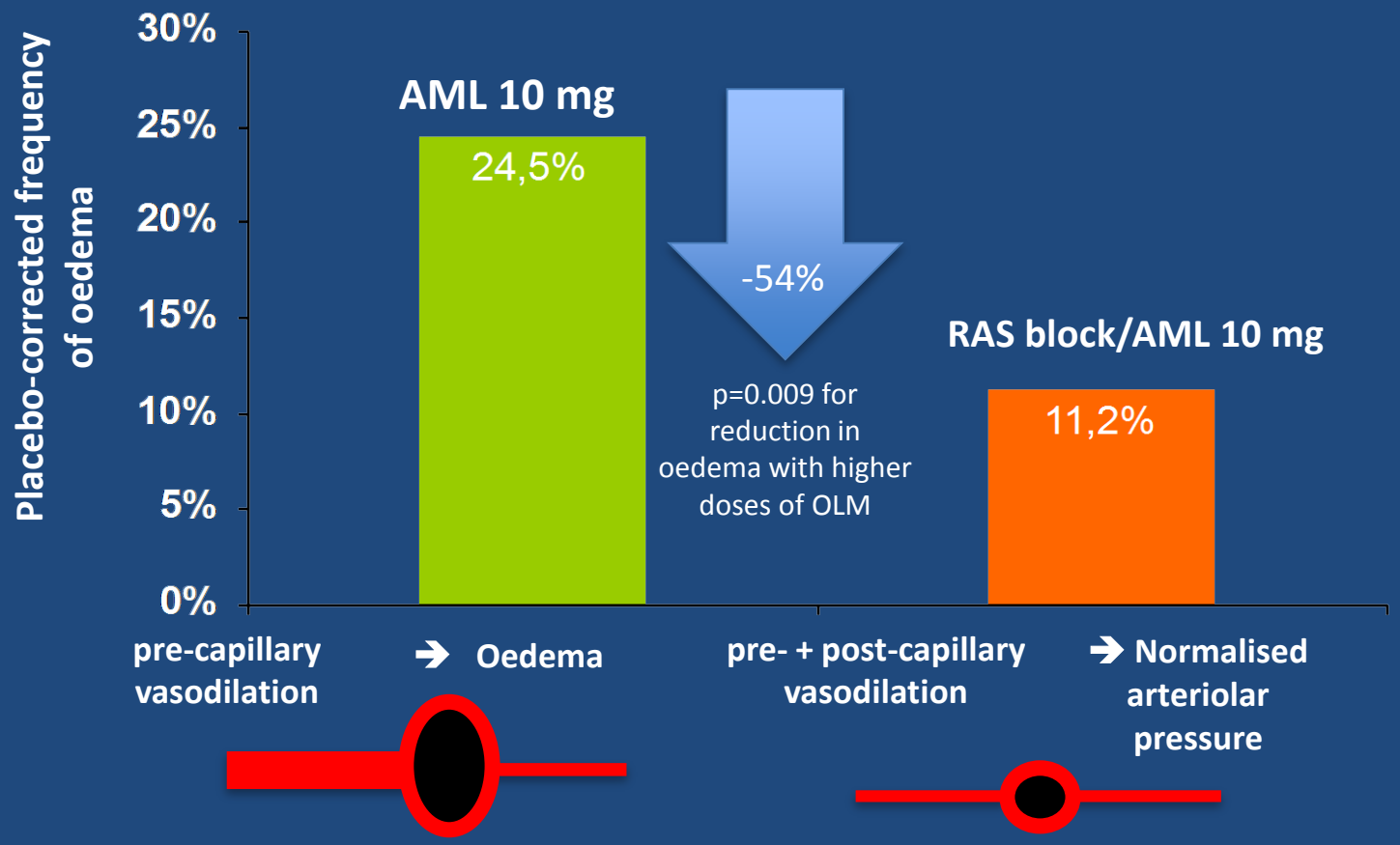


ACEI, angiotensin-converting enzyme inhibitor;
CCB, calcium channel blocker

Wald et al. Am J Med 2009;122:290-300

Combining ARBs with CCBs and diuretics gives synergistic reductions in adverse events

- **Reduces hyperglycaemic/diabetes with thiazides[1]**
- **Reduces oedema with CCBs[2]**



1. Alderman et al. J Hypertens. 2008 May;21(5):493-9, and Law et al. BMJ 2009;338:b1665.
2. Adapted from Chrysant et al. Clin Ther 2008;30:587-604 and Epstein et al. Drugs 2007;67:1309–1327.