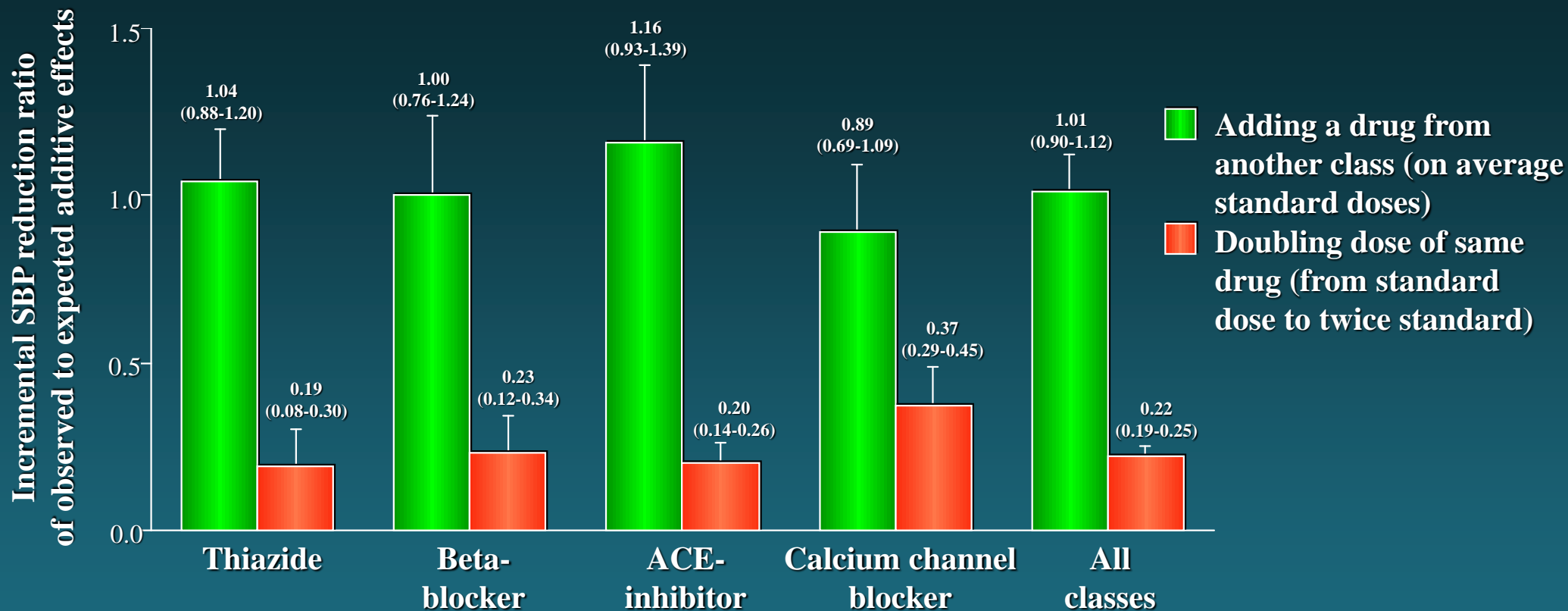


Combinazioni a dosi fisse nella terapia dell'ipertensione. Nuovi sviluppi.

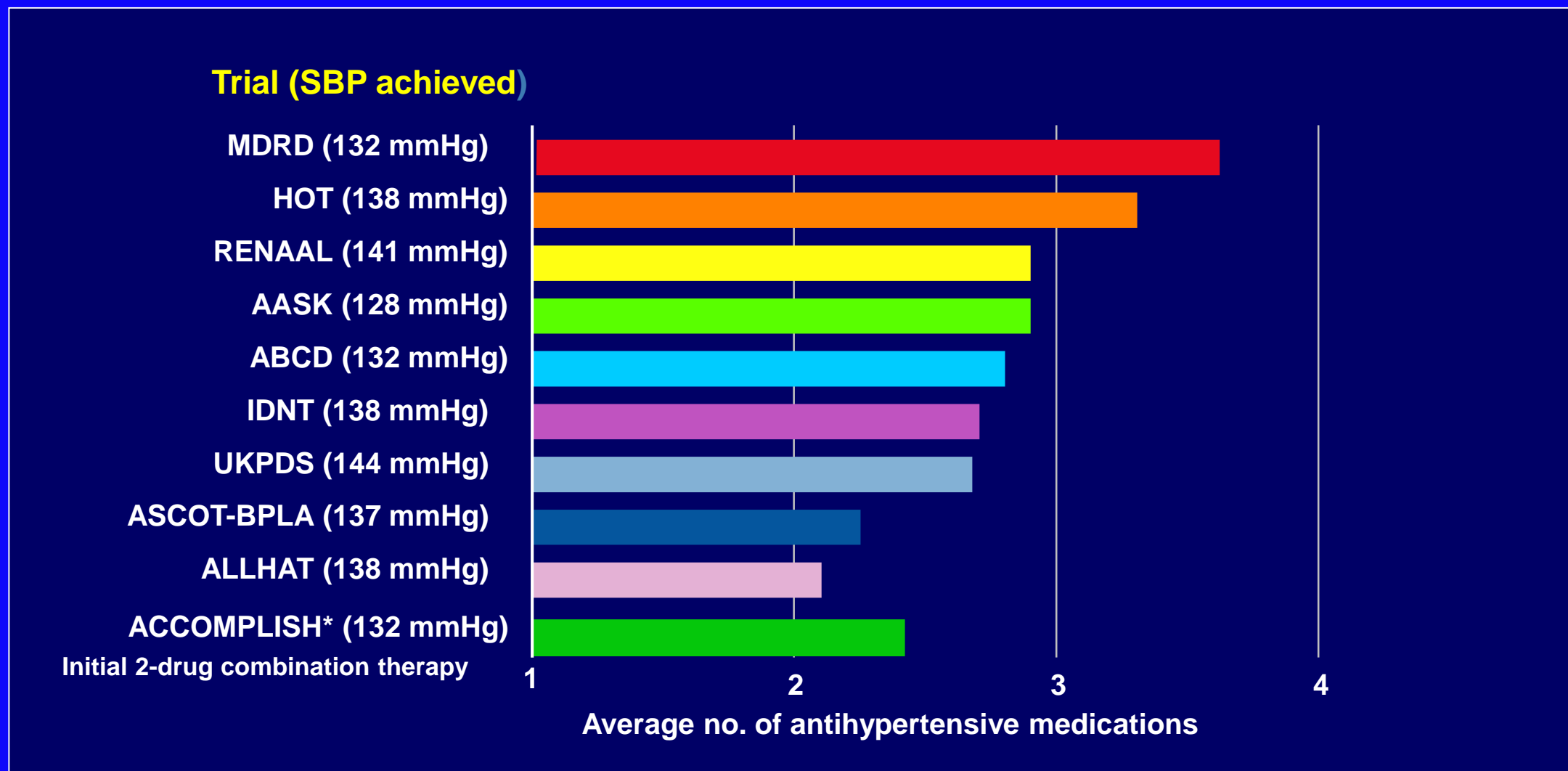
Giuseppe Mancina - Università Bicocca - Milano

Ratio of observed to expected incremental blood pressure-lowering effects* of adding a drug or doubling the dose according to the class of drug



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

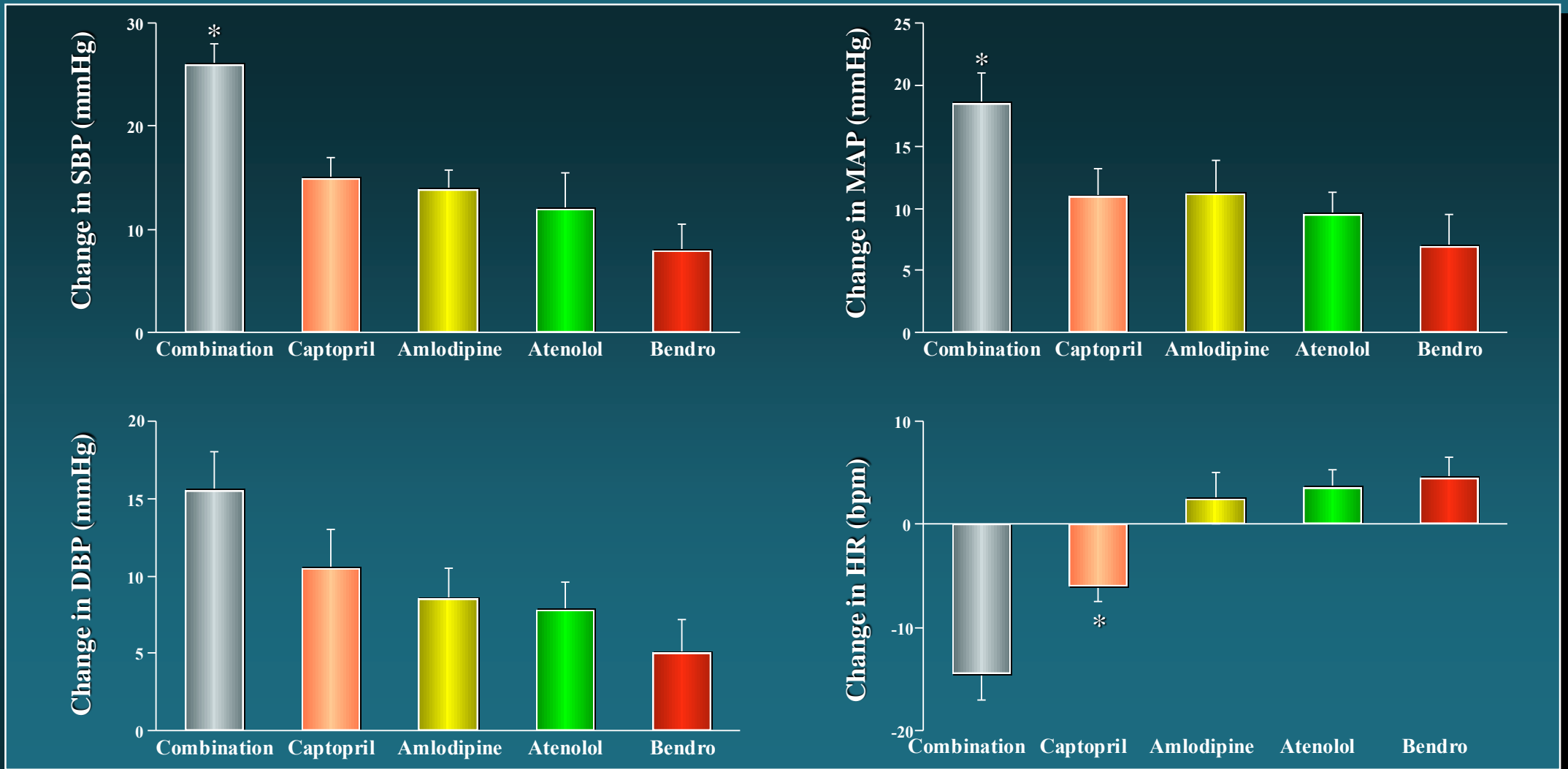
Average Number of Antihypertensive Agents Needed per Patient to Achieve Target BP Goals



Updated from Bakris GL, et al. Am J Kidney Dis. 2000;36(3):646-661; Arch Int med 2003;163:425-41

UKPDS = United Kingdom Prospective Diabetes Study; MDRD = Modification of Diet in Renal Disease; HOT = Hypertension Optimal Treatment; AASK = African American Study of Kidney Disease; RENAAL = Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; IDNT = Irbesartan Diabetic Nephropathy Trial

Changes in BP and HR in HT Patients Treated with Amlodipine, Atenolol, Bendroflumethiazide, Captopril or a Low-dose Quadruple Combination



Combination treatment

- No matter which drug is employed, monotherapy can effectively reduce BP in only a limited number of hypertensive patients
- Most patients require the combination of at least two drugs to achieve BP control

**In most countries most hypertensive pts are
treated with one drug:
-Up to maximal dose
-Sequential monotherapy**

Combination Treatment

When should combination treatment be used?

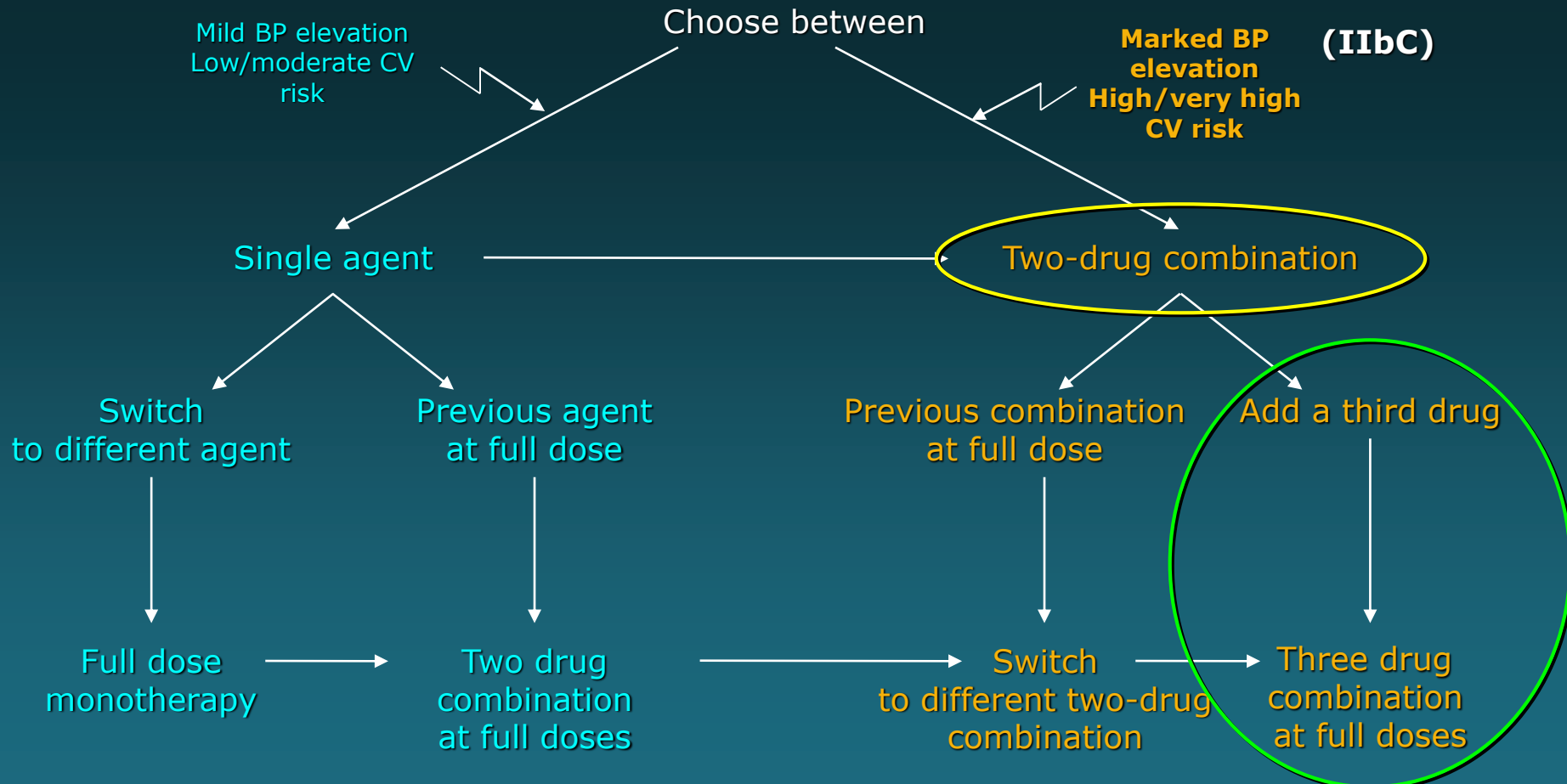
- **After ineffective monotherapy?**
- **As 1st step treatment?**

Two-drug combinations as initial Treatment /Cons

- **Unnecessary administration of a second drug in a number of patients (who would be controlled by monotherapy)**
- **Ascribing drug-related side effects more difficult**
- **Increased incidence of hypotension(and fall injuries), especially in grade 1 hypertension and in the elderly**

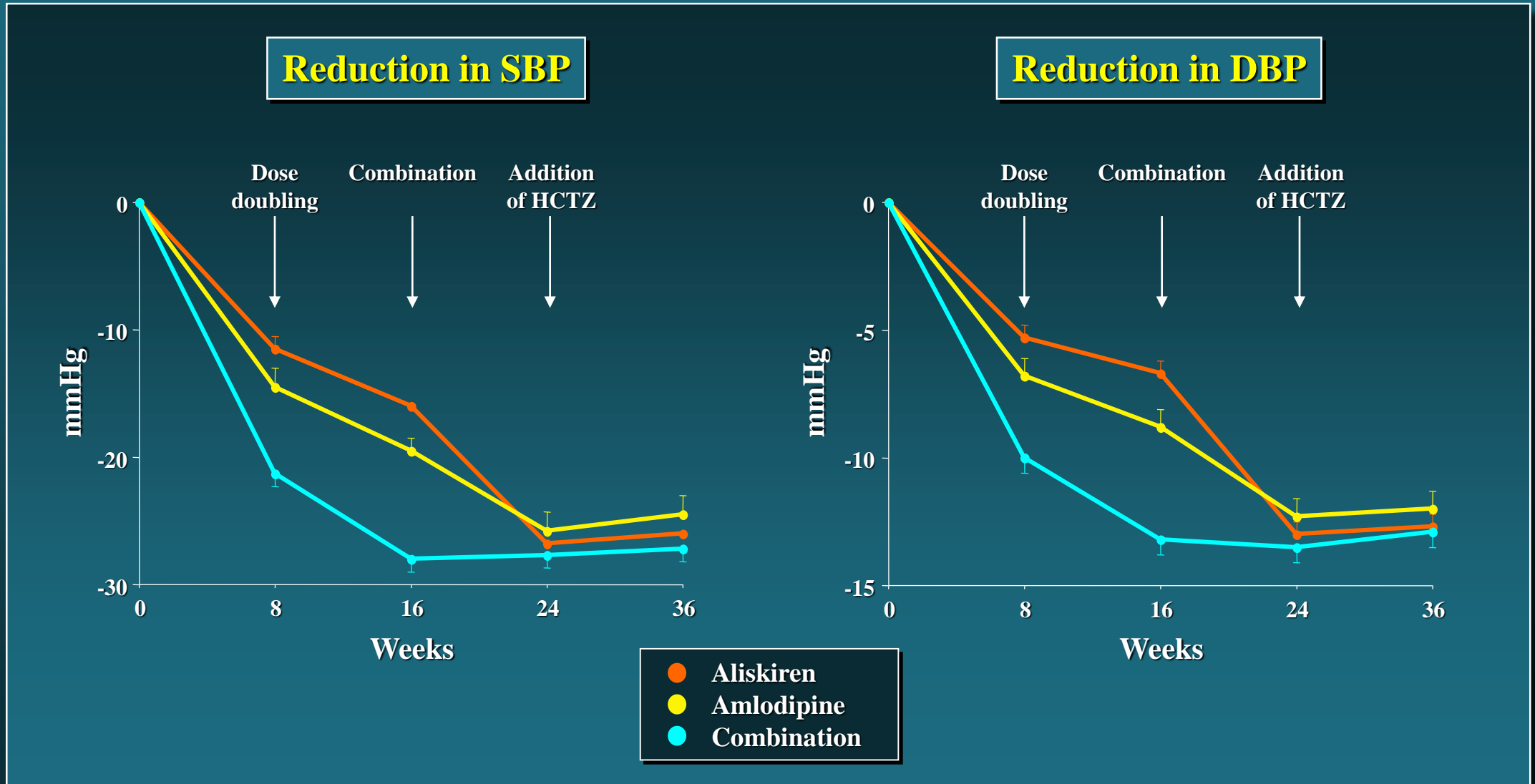
Mancia et al, J Hypertens 2017, 35,225

Monotherapy vs. drug combination strategies to achieve target BP



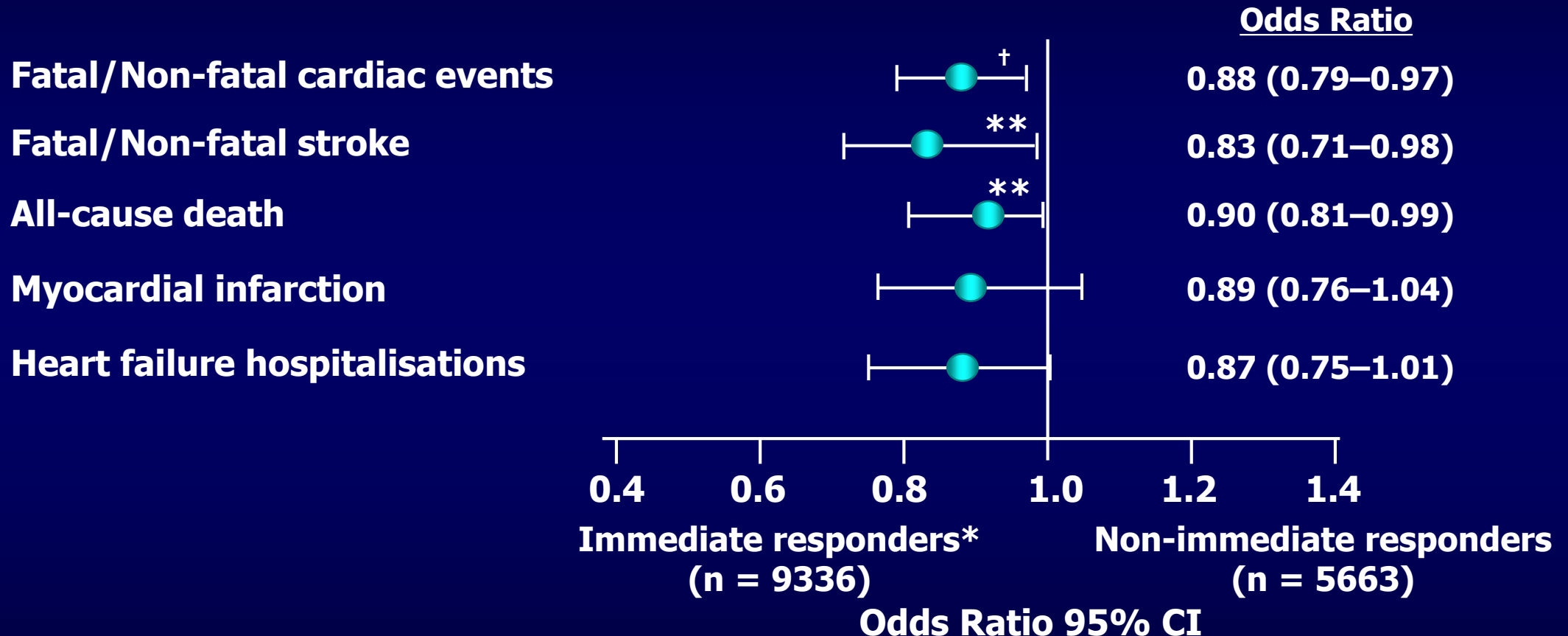
Moving from a less intensive to a more intensive therapeutic strategy should be done whenever BP target is not achieved.

BP Reductions by Initiating Treatment with Two Drug Combination (Aliskiren + Amlodipine) or the Combination Components in Monotherapy



VALUE: Analysis of Results Based on Immediate Response*

Pooled Treatment Groups

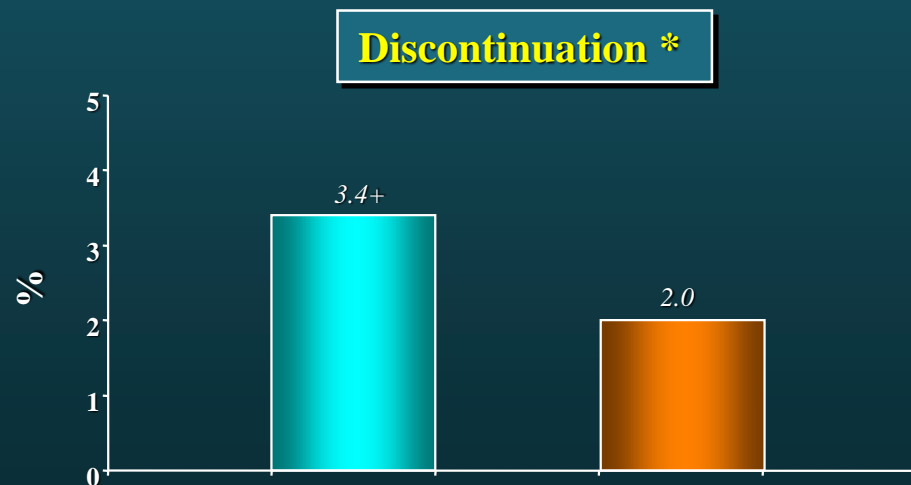
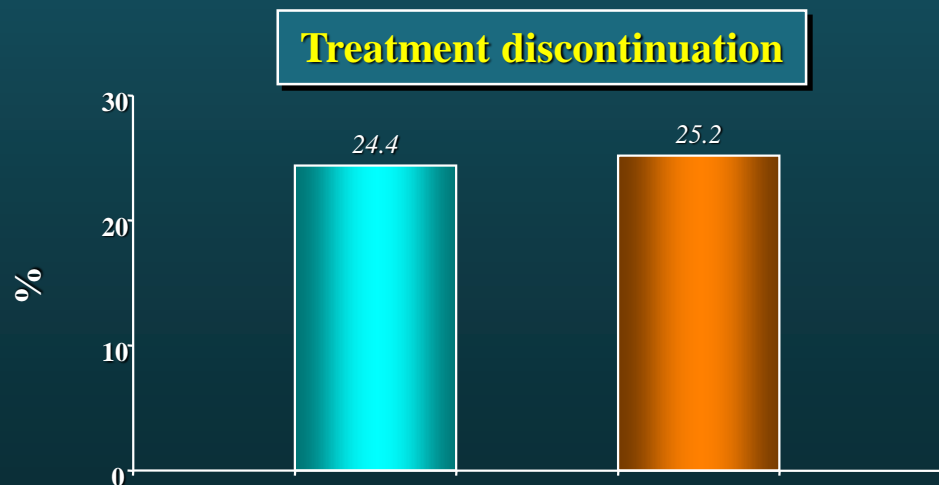
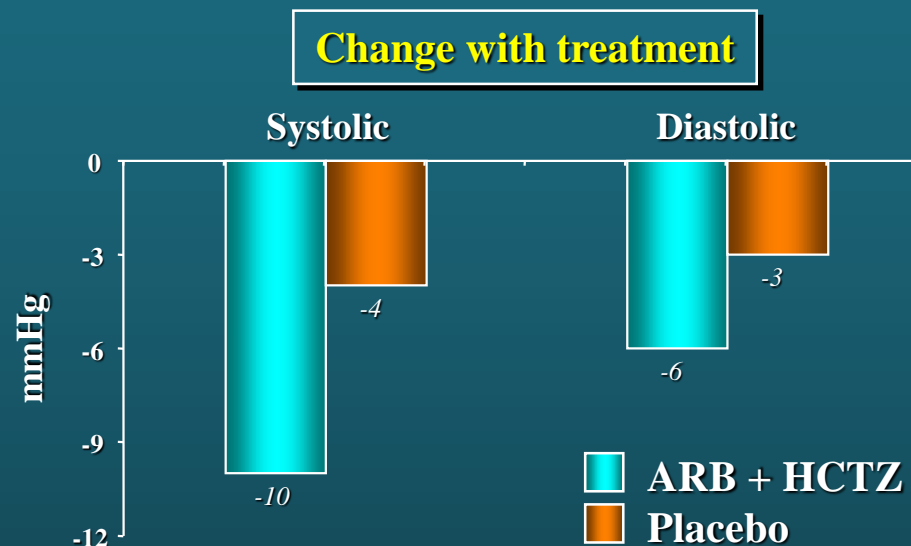
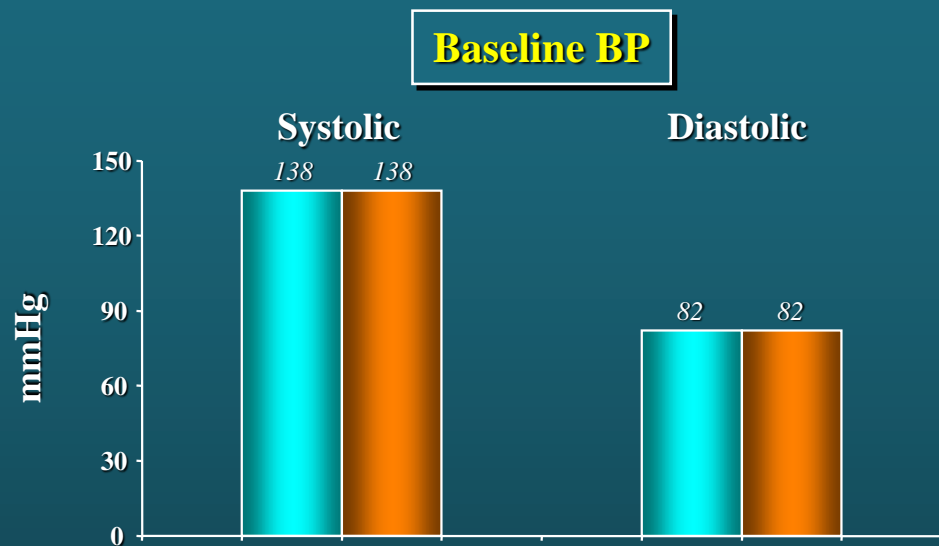


*Those not on previous tx: SBP ↓ ≥10 mmHg at one month;
those on previous tx: SBP ≤ baseline at one month.

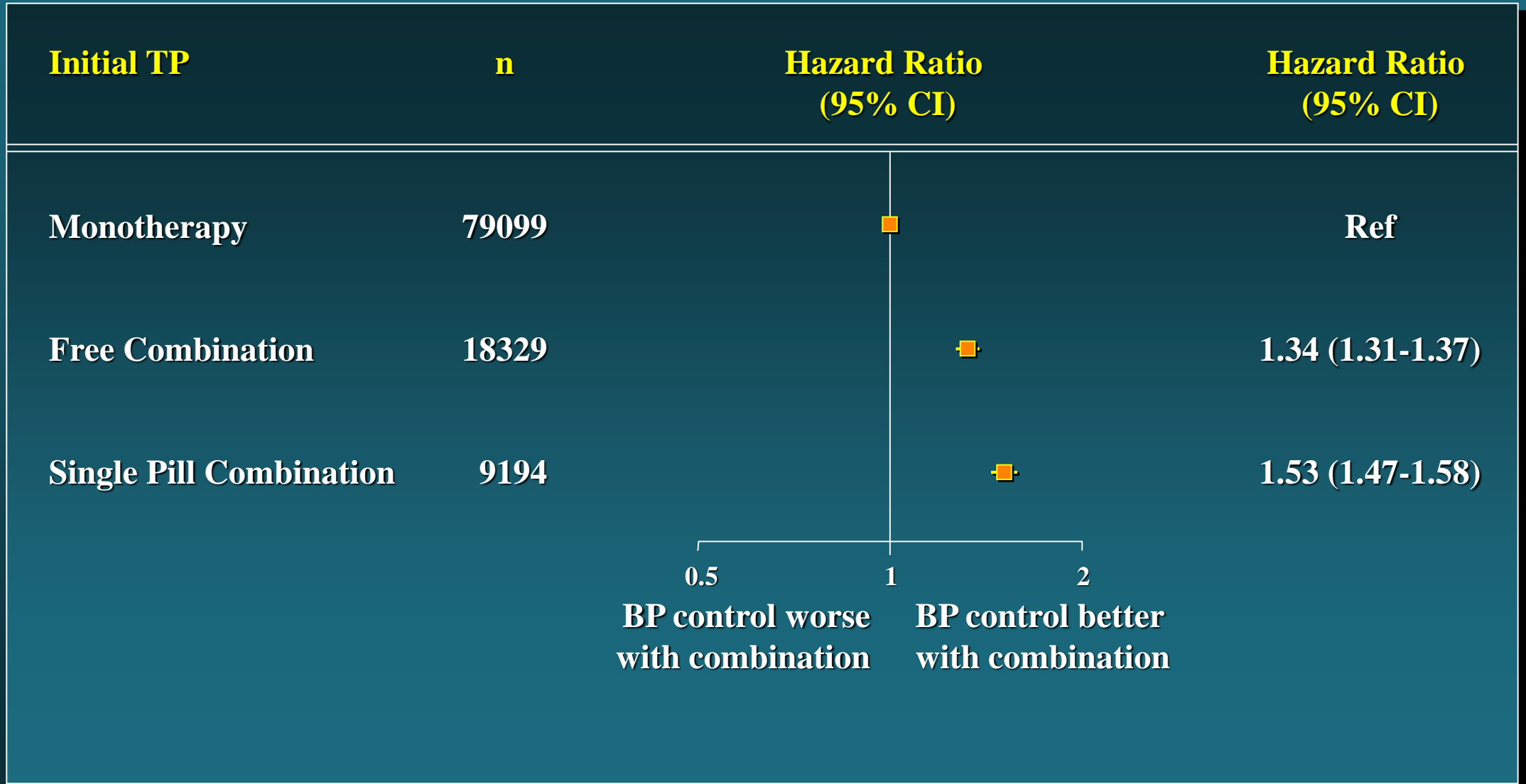
** $P < 0.05$; † $P < 0.01$.

Weber MA et al. *Lancet*. 2004;363:2047–49.

Blood pressure, treatment discontinuation and hypertension in HOPE-3



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

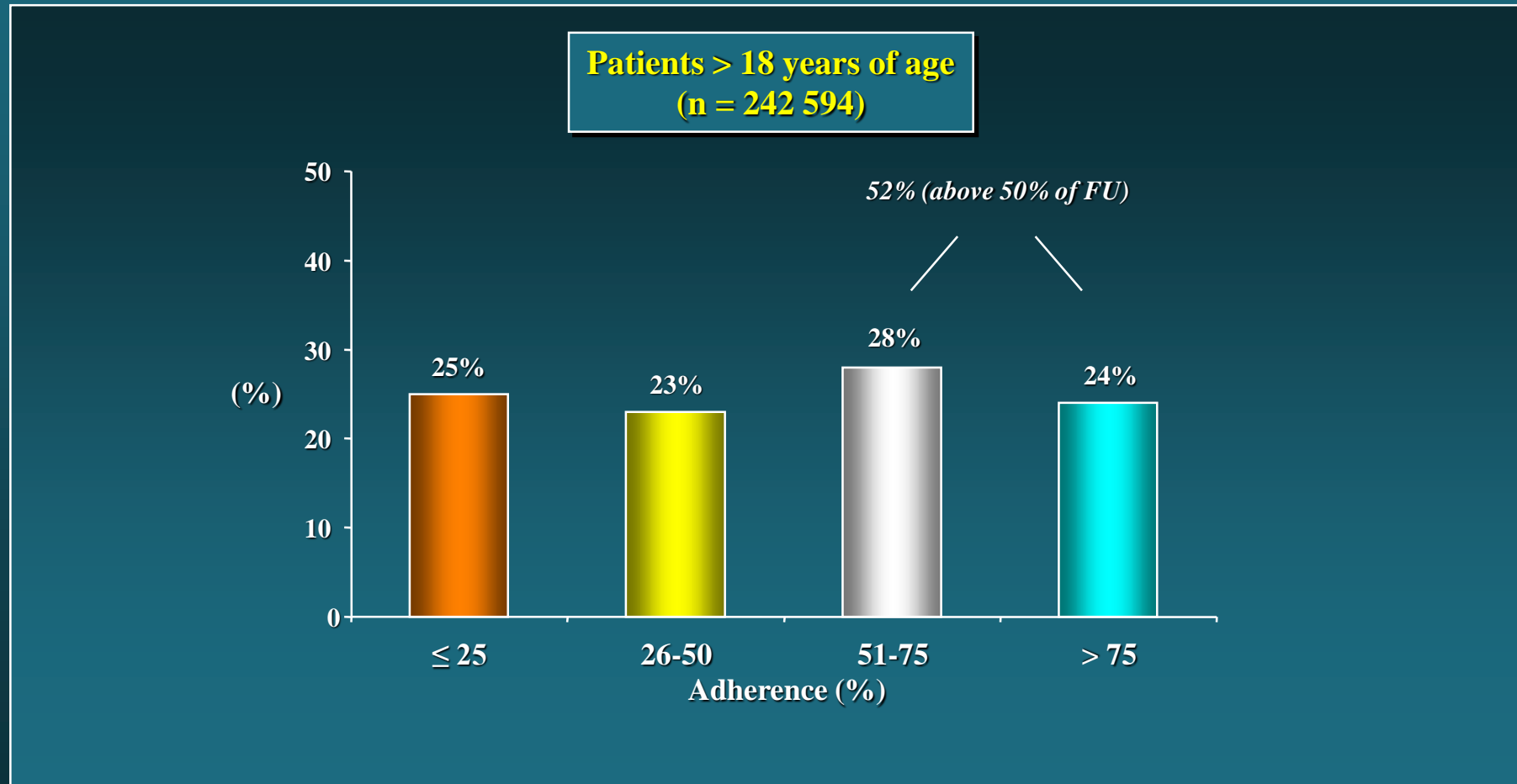


**Why is an initial monotherapy
free to adopt combination treatment later
less effective over the long-term?**

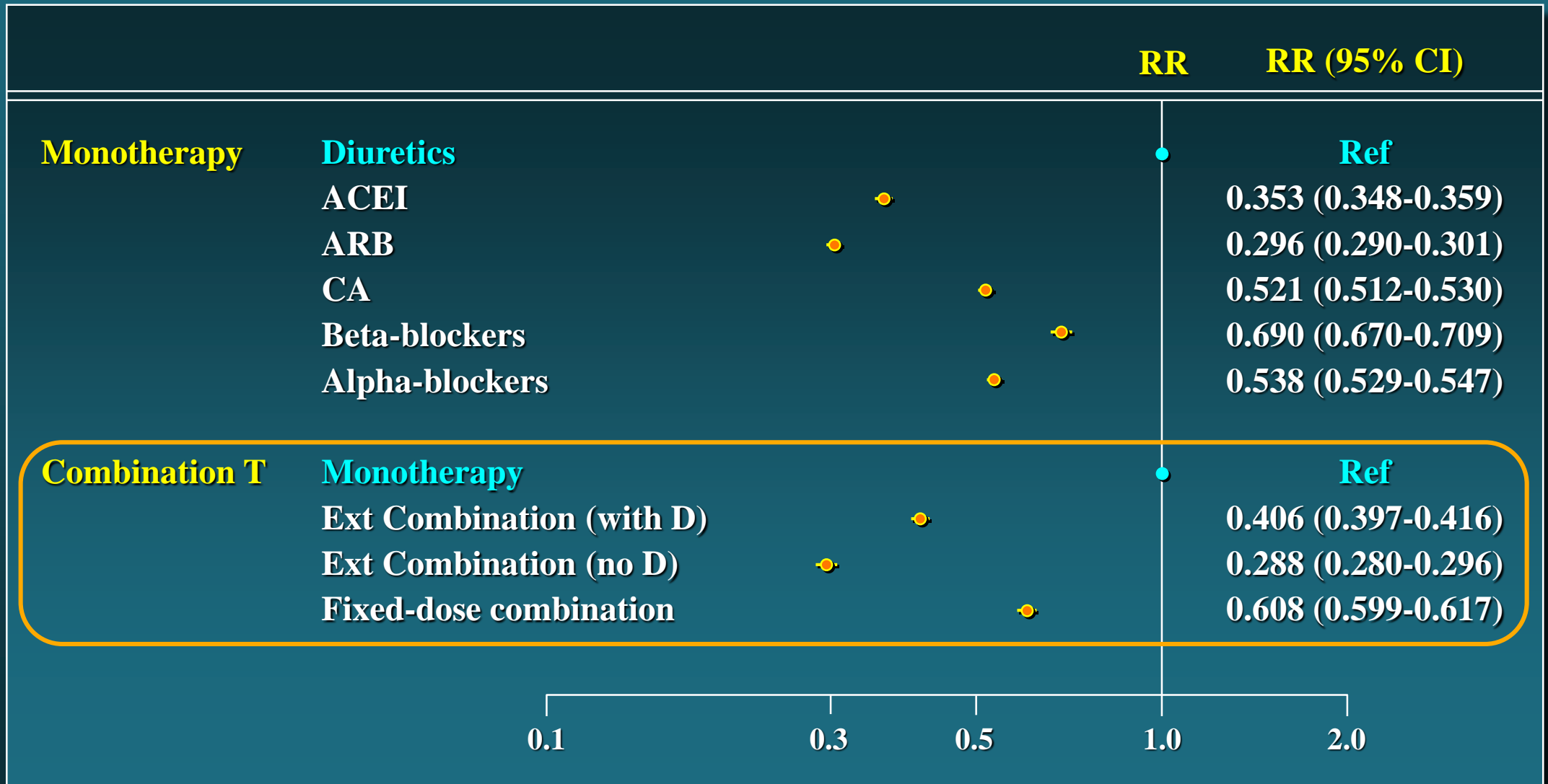
Measures /Discontinuation-Adherence

- **Discontinuation**, i.e. lack of renewal of drug prescription over ≥ 90 days following expiration of the previous prescription
- **Adherence**, i.e. percent of time covered by drug prescription divided by overall follow-up time

Adherence (% of FU time covered by prescription) to antihypertensive drug treatment in a Lombardy cohort



Relationship between risk of Discontinuation of antihypertensive treatment and initially prescribed drugs (n=433680)

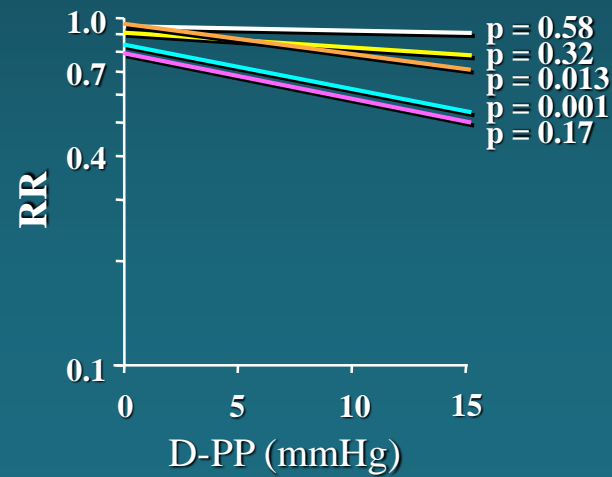
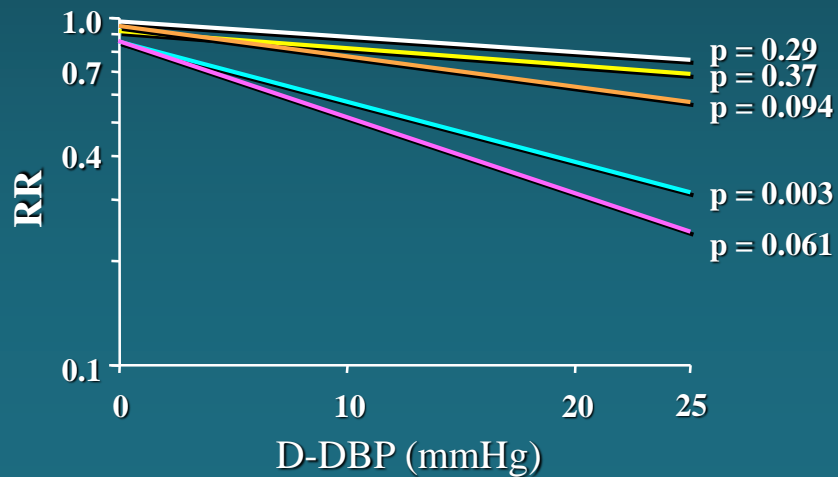
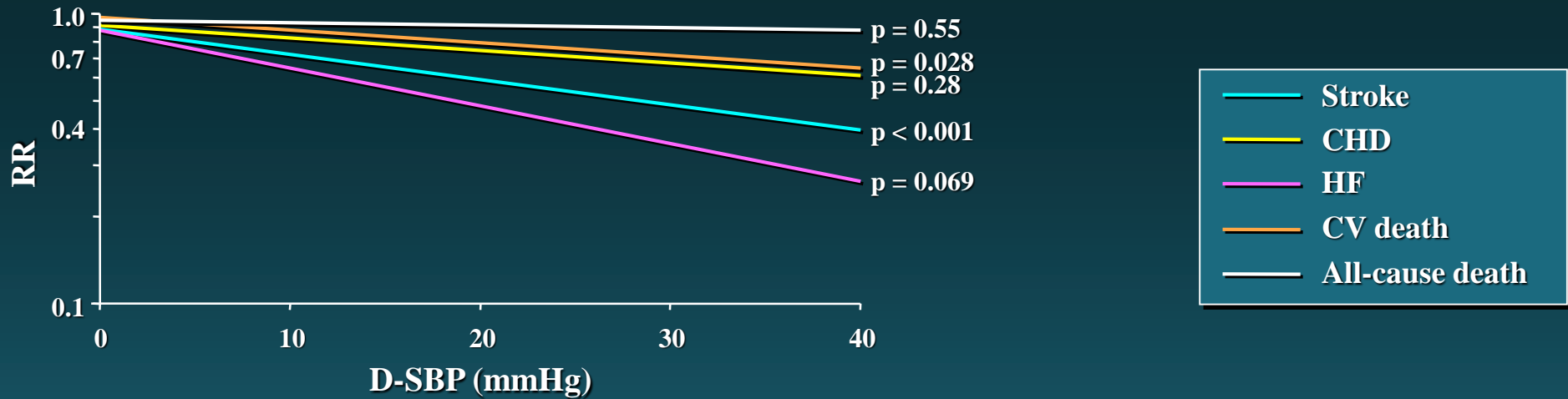


Psychological impact of a prompter BP control

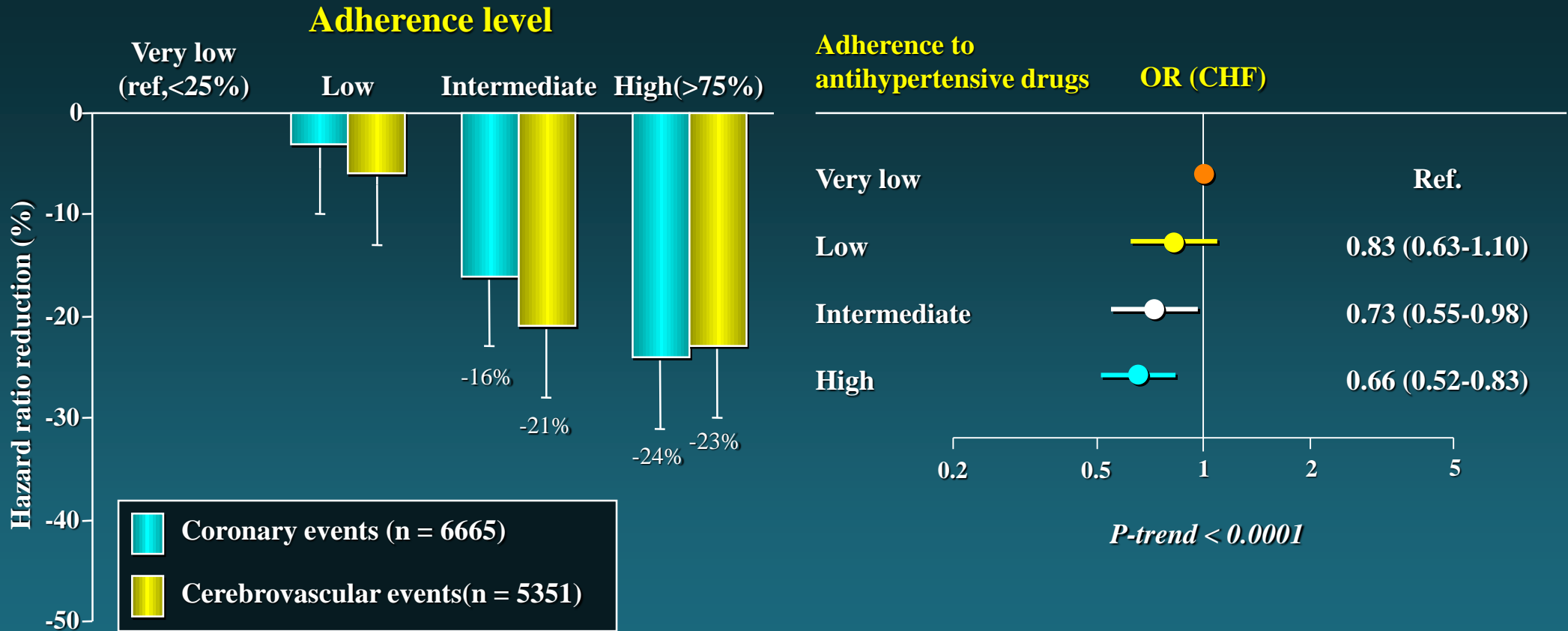
- **Greater confidence in the doctor and his/her advices**
- **Relief of disease-dependent stress**
- **Greater motivation to continue treatment**

Note: the above effects can be seen much more in real life medicine than in trials

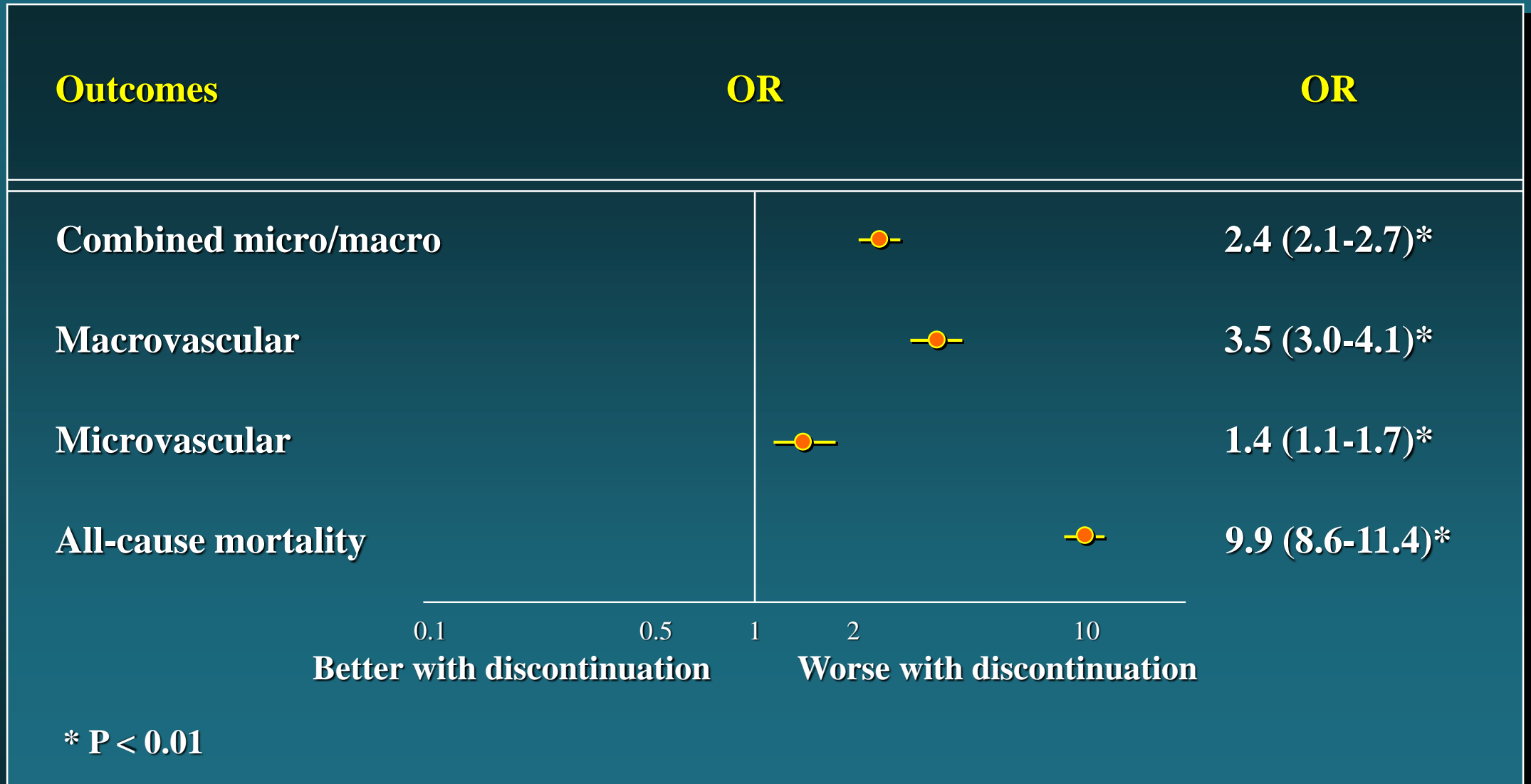
Relationship of Outcome Reduction to Extent of BP Reductions in BP-lowering Trials (intentional BP reduction trials in hypertensive patients)



Effects of Adherence to Antihypertensive Drug Therapy on the Risk of Coronary and Cerebrovascular Outcomes in 242.594 Patients and on the Risk of HF (Lombardy data-base)

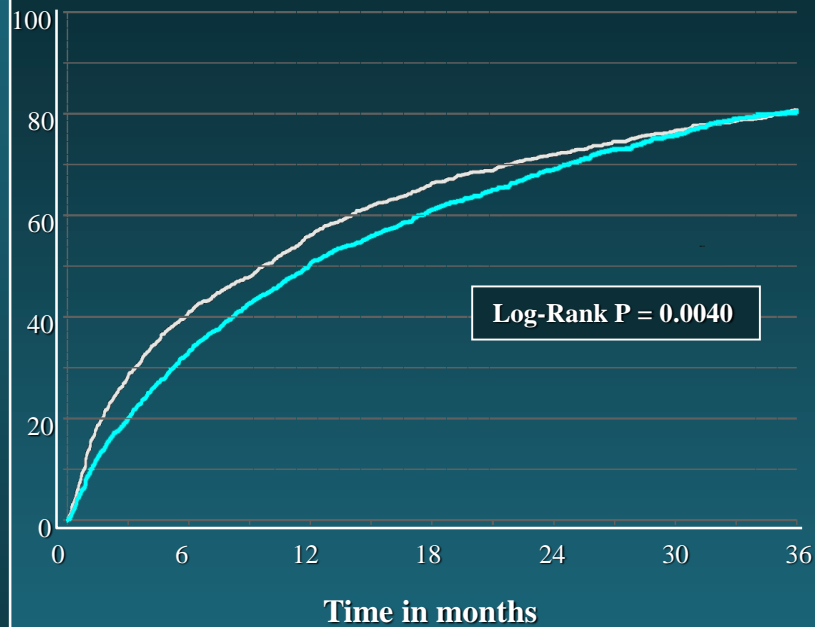


Adjusted Risk of Outcomes (and 95%CI) after Permanent Discontinuation (active treatment and placebo pooled)



K-M Estimates of Achieving Target BP for Each Exposure Group - Incidence Rates and Ratios of CV Events

% of patients reaching target BP



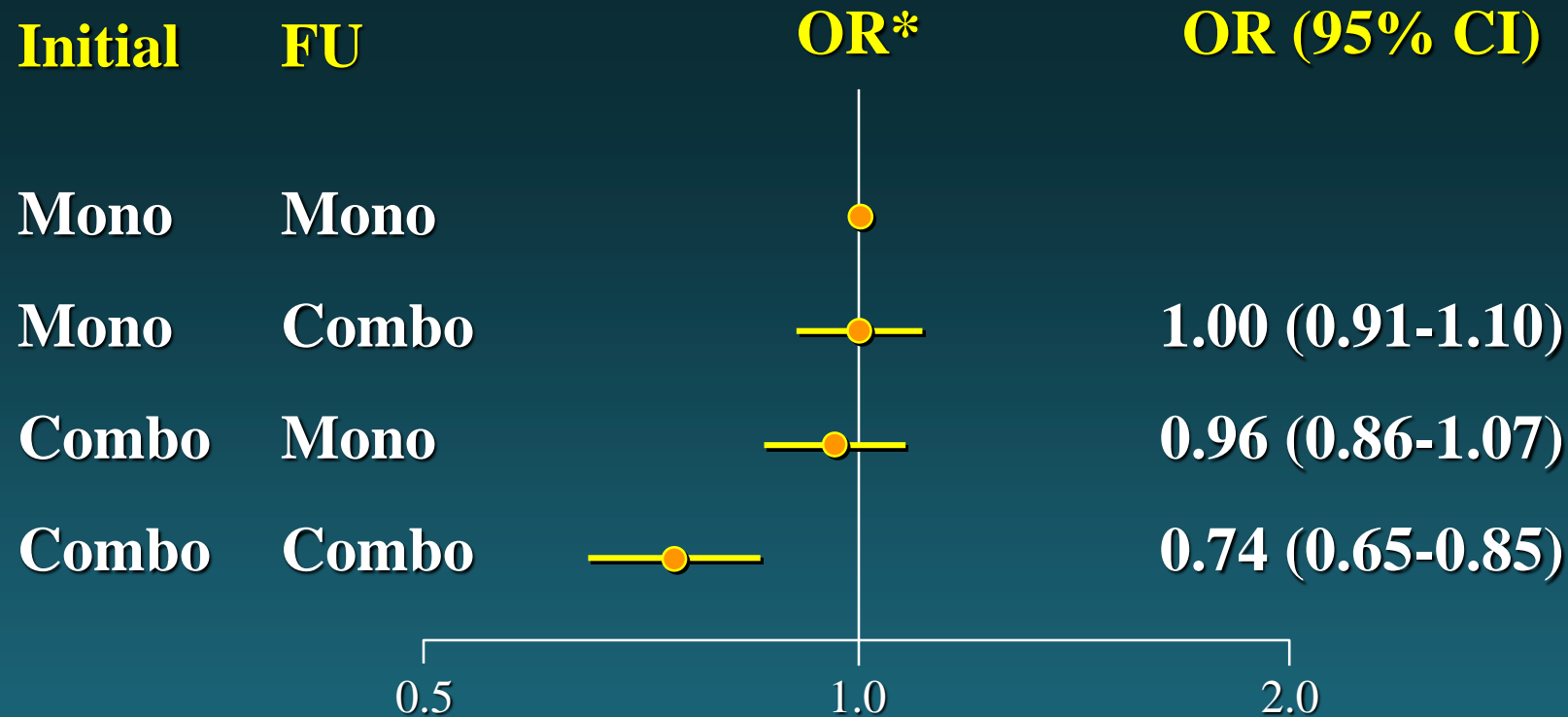
— Combination therapy
— Add-on

	Incidence Rate (Combination T vs. Add-on)	IRR (95% CI)	P-Value
Acute MI	0.45 vs. 0.99	0.19 (0.10-0.34)	<0.0001
Stroke/TIA	2.57 vs. 2.84	0.79 (0.59-1.06)	0.1172
Hospitalization for Heart Failure	0.55 vs. 0.78	0.54 (0.31-0.95)	0.0311
<i>Overall</i>	3.34 vs. 4.10	0.62 (0.48-0.80)	0.0002
<i>Overall (With Death)</i>	3.58 vs. 4.28	0.66 (0.52-0.84)	0.0008

0 0.25 0.5 0.75 1.0 1.25

Combination T better Add-on better

Effect of Initial and Subsequent BP Lowering Strategies on Coronary / Cerebrovascular Risk (n = 209650)



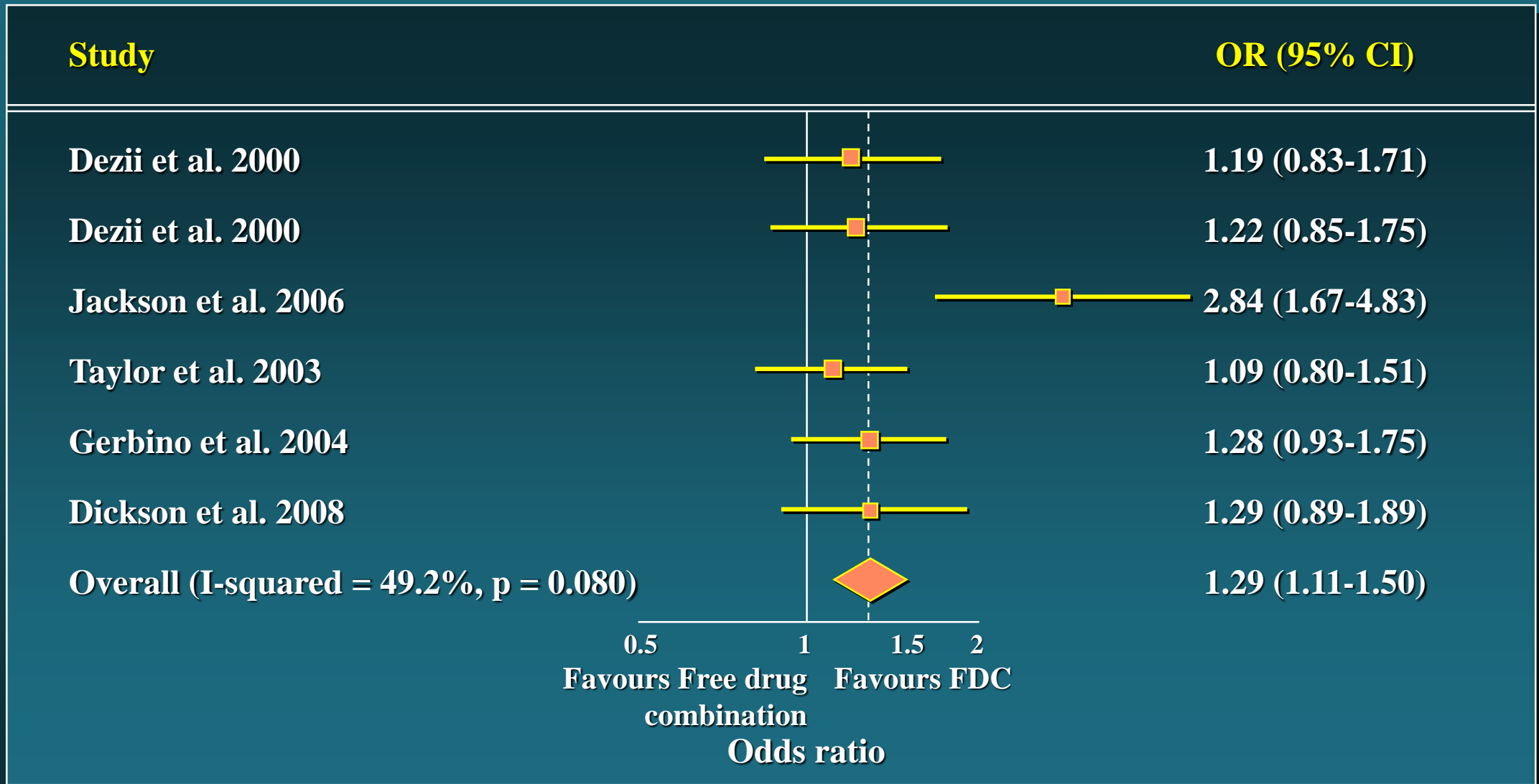
* Adjusted for age / gender / number of BP lowering drug classes during FU / concomitant use of drugs for CHF / CAD / diabetes etc

**Free dose
or
fixed dose (single tablet)
drug combinations?**

Disadvantages of Fixed-dose Combinations

- Lower flexibility in the drug titration phase
- Attribution of side effects more difficult
- Greater risk of administering a contraindicated drug
- If treatment stops suddenly all effect is lost
- Pharmacokinetic irrationality of some fixed-dose combinations

Compliance and Persistence with Therapy with Use of an FDC as Compared to Its Free-drug Combination



Improved Compliance to Treatment with Fixed-dose Combinations of Antihypertensive Drugs

- At all ages**
- At all background number of pills**
- With / Without concomitant CV / non-CV diseases**
- Improvement maintained/increased with time**

Fixed-dose Combinations

- «As in previous GLs the 2013 ESH/ESC GLs favour use of two antihypertensive drugs at fixed doses in a single tablet»
- «Reducing the number of pills to be taken daily improves adherence, which is low in hypertension, and increases the rate of BP control»
- Reduced flexibility during treatment up-down titration attenuated by availability of FDCs with different doses of components

How many and which drugs in FDC?

- - RAS blocker (ACEI or ARB) + CCB
- RAS blocker (ACEI or ARB) + D
- D + CCB
- BB + D or CCB
- ACEI + B
- 2) - D + CCB + RAS blocker (Triple T)
- 3) -Quadipill (4 drugs at $\frac{1}{4}$ dose each)

Most patients have overlapping CV Risk Factors

Multiple Comorbidities

Increases Risk 400% to 700%

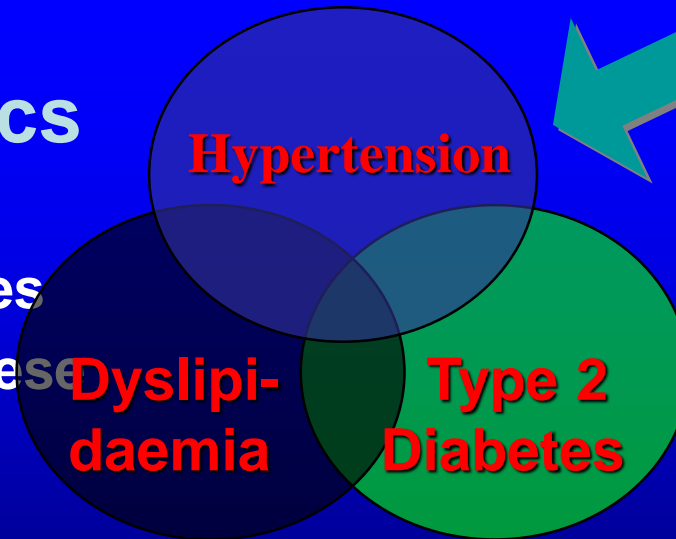
Of all hypertensives

- 65% have dyslipidaemia
- 16% have type 2 diabetes
- 45% are overweight/ obese



Of all dyslipidaemics

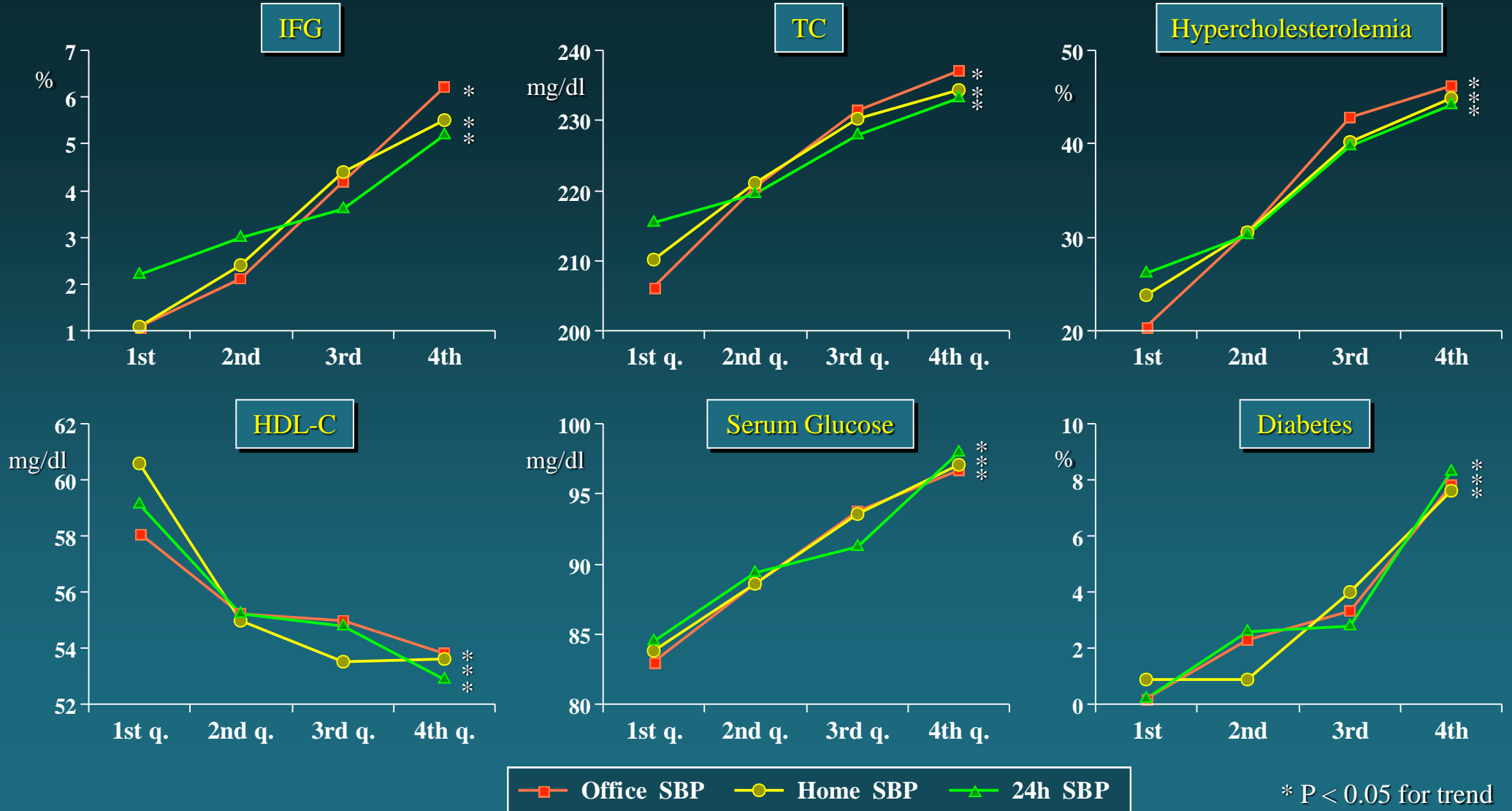
- 48% have hypertension
- 14% have type 2 diabetes
- 35% are overweight/ obese



Of all type 2 diabetes

- 60% have hypertension
- 60% have hyperlipidemia
- 90% are overweight/ obese

Relationship between Metabolic Risk Factors and Office, Home, 24h SBP Quartiles



Interaction between Risk Factors for CHD risk (MRFIT)

● Highest cholesterol quintile	11.2	}	21.9
● Highest BP quintile	10.7		
● Highest BP+ Cholesterol quintile	30.3		
● Interaction			+ 38.4%

Proportion of Patients Discontinuing “CV Prevention” Drug Treatment after Expiration of Initial Prescription in Lombardy

Antidiabetics

Antilipids

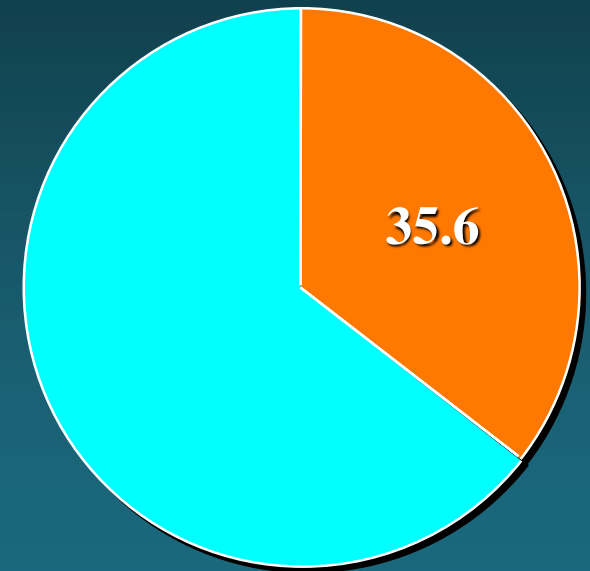
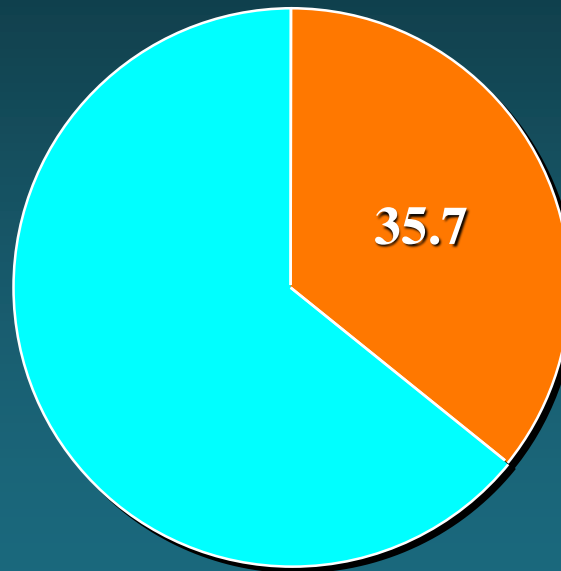
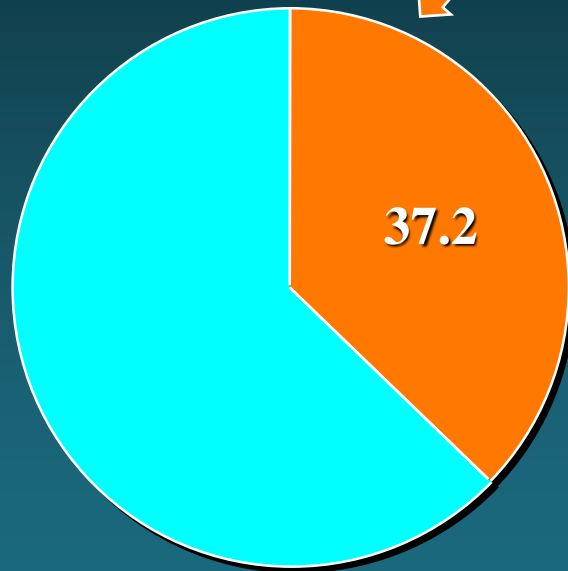
Antihypertensives

Treatment
discontinuation

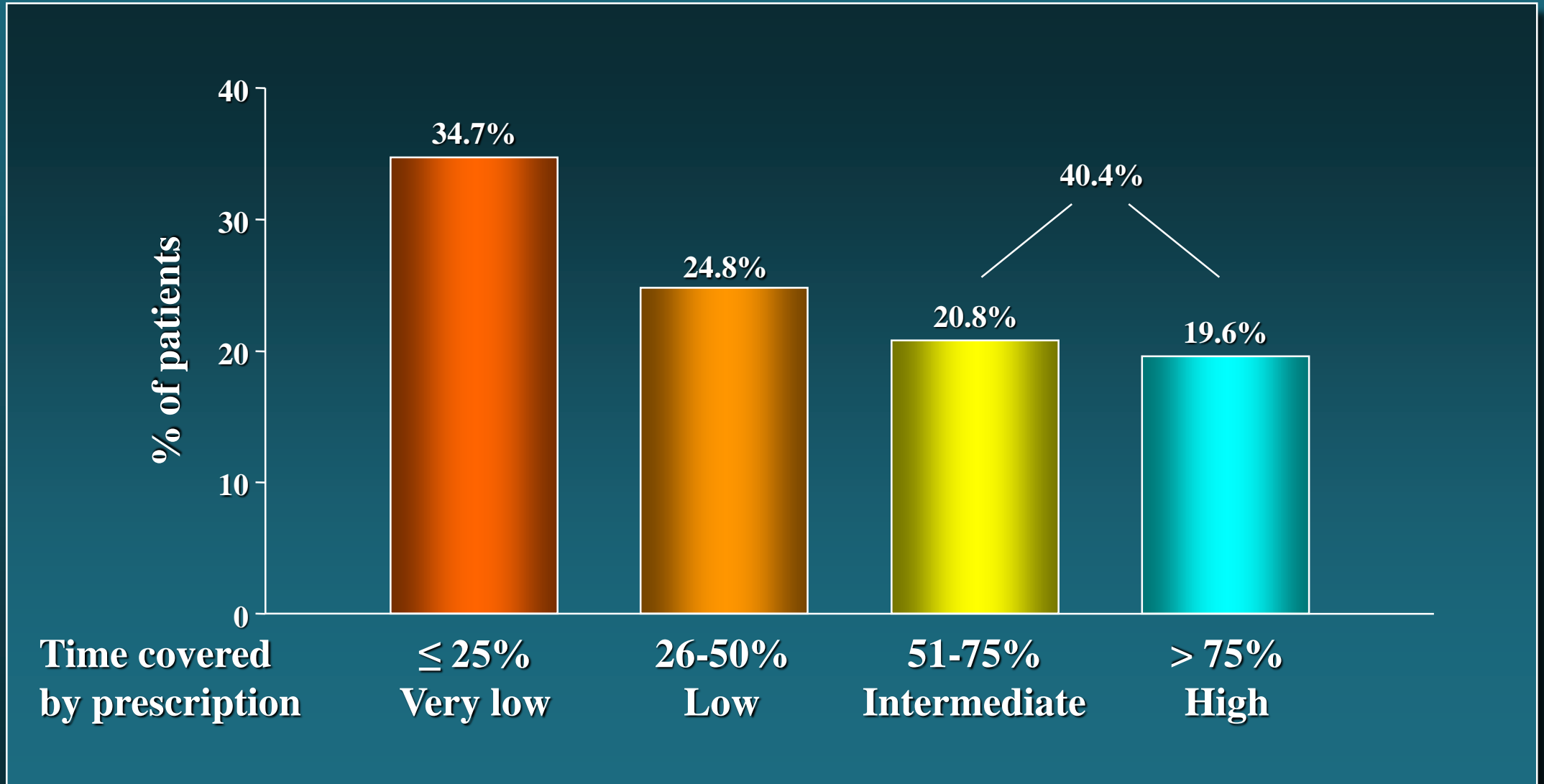
37.2

35.7

35.6



Adherence to Statin Treatment in Lombardy Data-base (n = 90832 / 2002-2007)

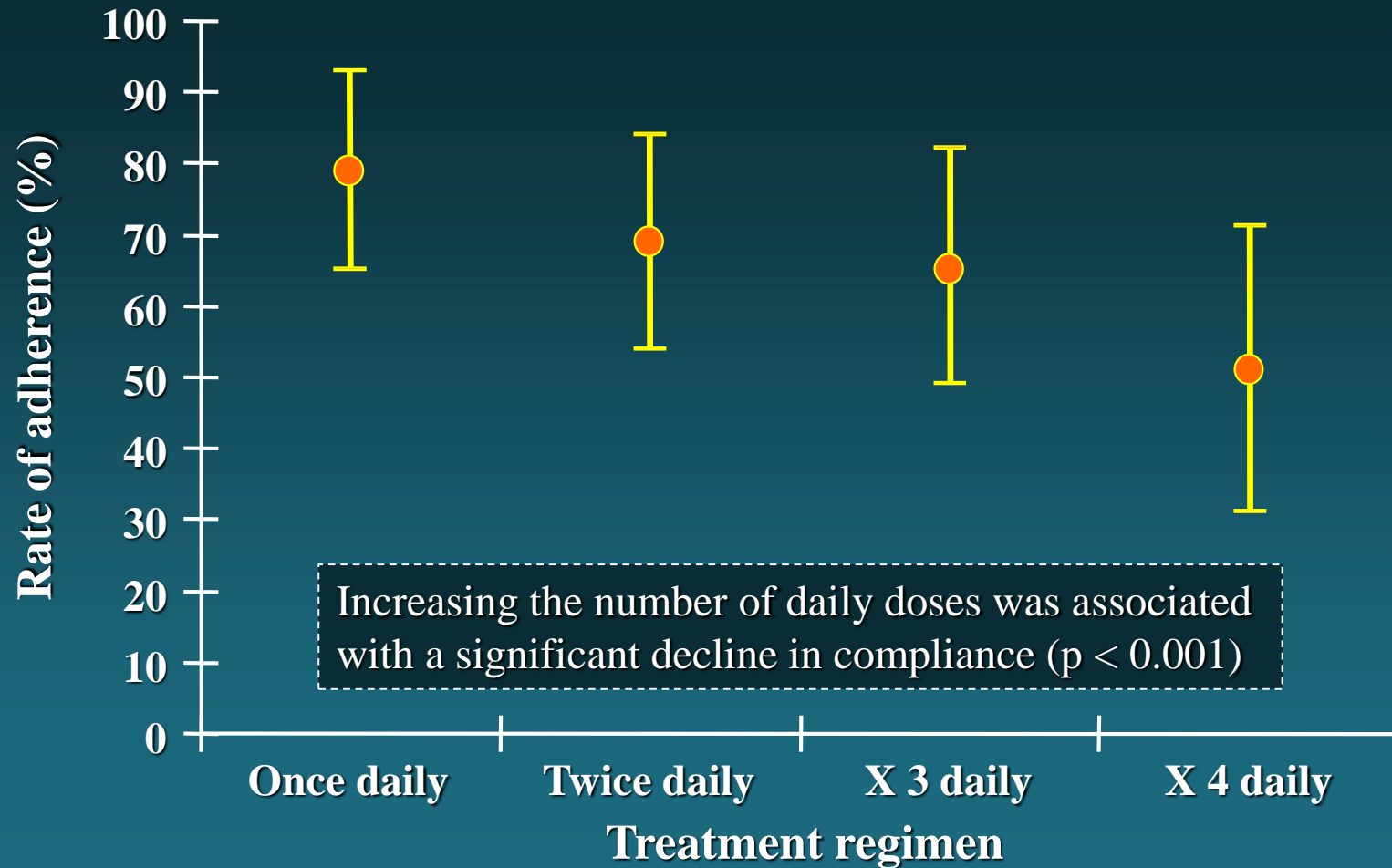




“Polypill”???

© 2006 Barry J. Materson, MD, MBA

Compliance vs Pill Burden (76 studies/electronic monitoring)



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

Coca A¹, Aqabiti-Rosei E, Cifkova R, Manolis AJ, Redón J, Mancia G.

⊕ Author information

Abstract

: Antihypertensive, lipid lowering, antidiabetic and antiplatelet treatments all substantially reduce the risk of cardiovascular morbid and fatal events. In real life, however, effective implementation of these treatments is rare, and thus their contribution to cardiovascular prevention is much less than it could be, based on research data. This article reviews the pros and cons of cardiovascular prevention by the polypill approach. It is argued that the high prevalence of individuals with a multifactorial risk profile provides a strong rationale for a therapeutic strategy based on the combination in a single tablet of drugs against different risk factors. It is further argued that other important favourable arguments exist. First, in real-life adherence to all above treatments is very low, leading to a major increase in the incidence and risk of cardiovascular outcomes. Second, although a large number of factors are involved, adherence is adversely affected by the complexity of the prescribed treatment regimen and can be considerably improved by treatment simplification. Third, recent studies in patients with a history of manifest cardiovascular disease have documented that different cardiovascular drugs can be combined in a single tablet with no loss of their individual efficacy or unexpected inconveniences and this does favour adherence to treatment and multiple risk factor control, supporting use of the polypill in secondary cardiovascular prevention. It is finally also mentioned, however, that the polypill may have some drawbacks and that at present no evidence is available that this approach reduces cardiovascular outcome to a greater degree than standard treatment strategies. Trials are under way to provide an answer to this question and thus allow the therapeutic value of this approach to be known.

Polypill/Possible inconveniences

- **Mismatching of drugs for quantity/efficacy/duration**
- **Titration to multiple targets more difficult**
- **Contraindication/side effects to one component lead to discontinuation of all protective treatments**
- **Missed dose(s)/other types of low adherence leave patient entirely unprotected**
- **May favour unhealthy lifestyles (?)**
- **No RCT evidence on extent of CV protection**

Polypill/Which is the optimal composition?

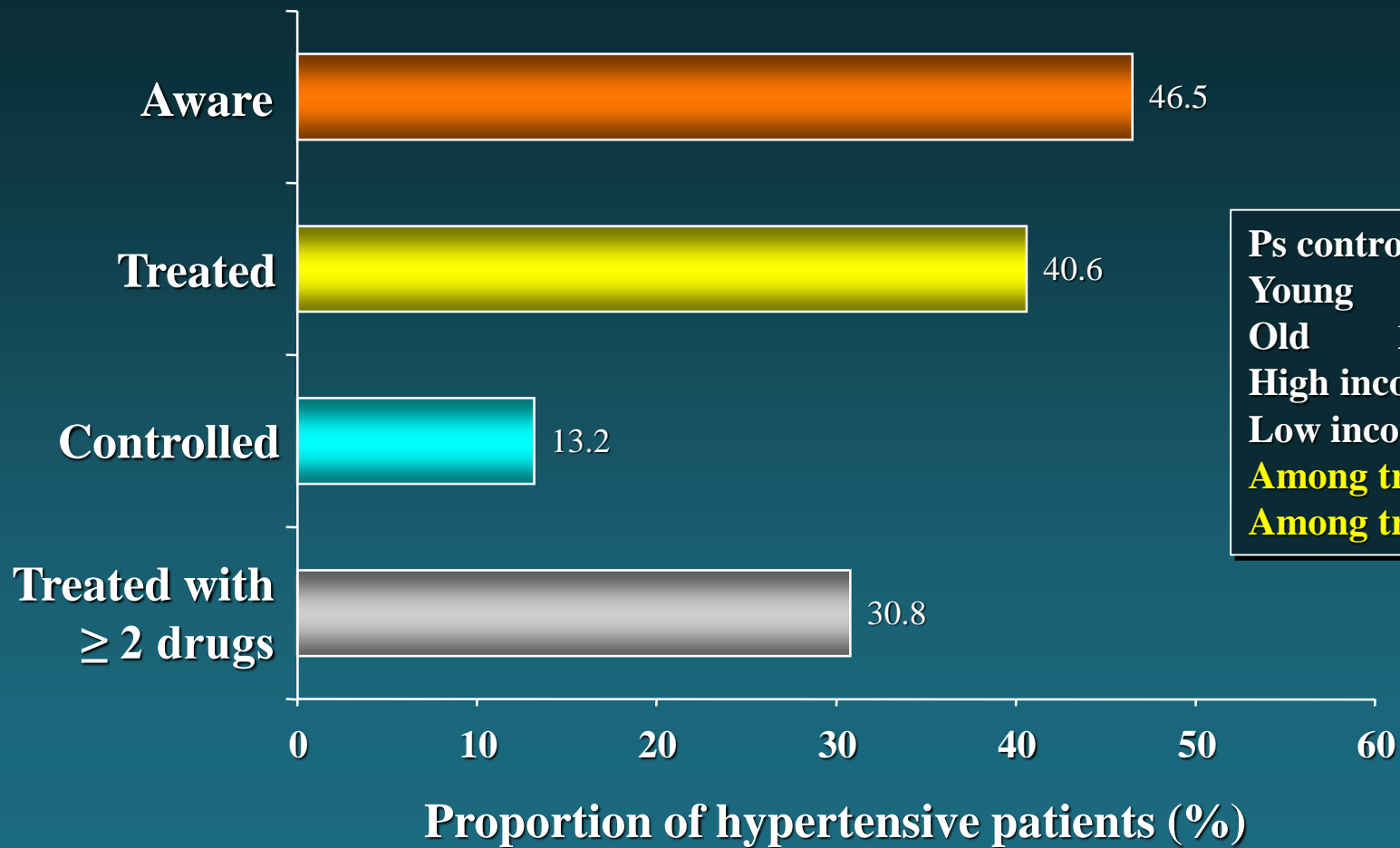
- **Less or more potent drugs?**
- **Lower or higher drug doses?**
- **Two or three antihypertensive drugs?**
- **Which antihypertensive drugs? Should a BB or Diuretic be included?**
- **Should aspirin be a component?**
- **Can we consider polypills with antidiabetic drugs?**
- **Vit E? Folic Acid? Others?**

Polypill/Questions

- Substitution therapy or independent treatment approach?
- All individuals aged 55ys or older(vaccination approach)?
- Secondary CV prevention?
- Primary prevention in high CV risk subjects?
- Subjects with multiple risk factors even if not high risk?
- Can it usefully replace complex treatments in unstable conditions, e.g. CKD?

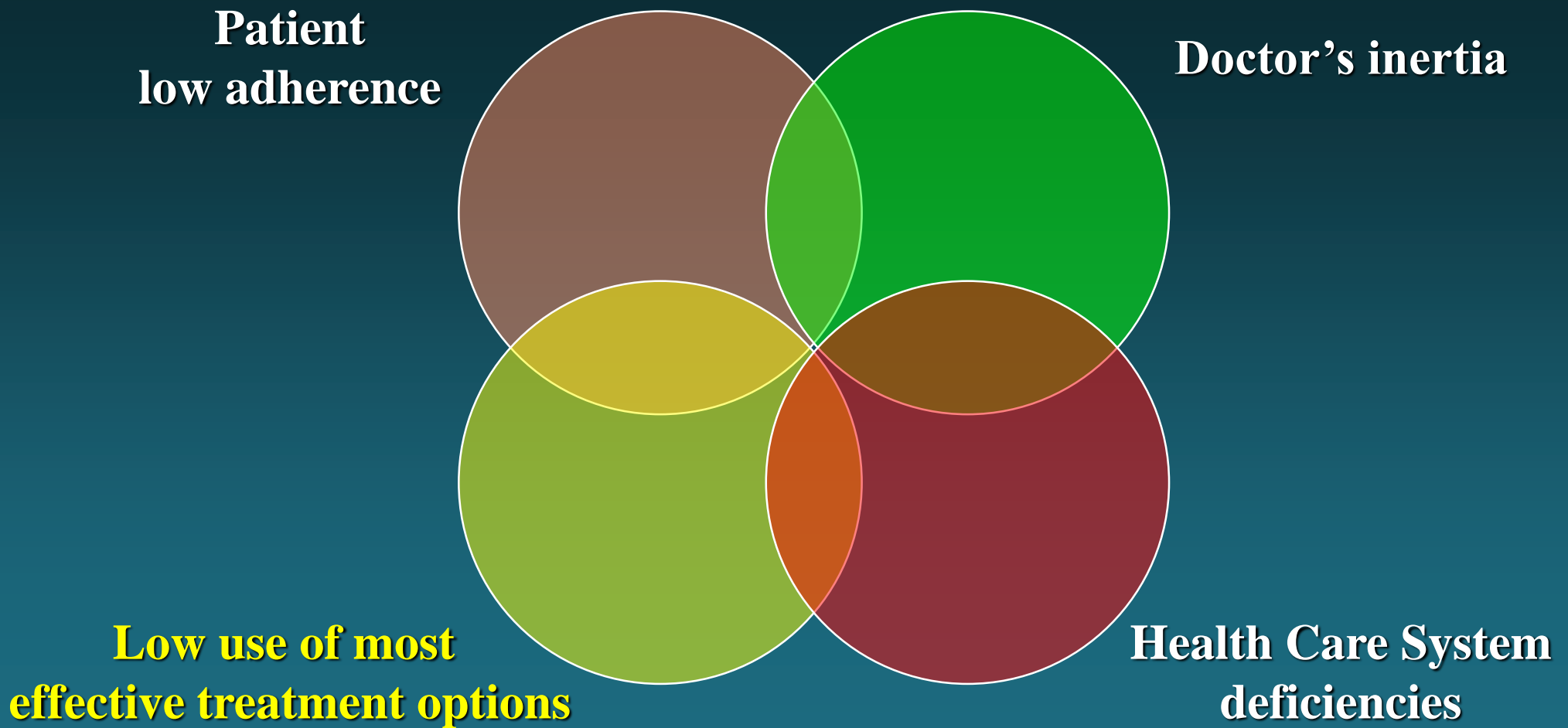
Coca, Mancia et al, J Hypertens, 2017

Proportion of Patients Aware / Treated and Controlled for Hypertension Prevalence in PURE (n = 142042 / Hypertension: 40.8%)



Ps control (4%)
Young 9%
Old 13%
High income 19.0%
Low income 12.7%
Among treated men 30.4%
Among treated women 33.8%

Major barriers to control of elevated BP in real life



INITIAL MONO vs COMBINATION TREATMENT IN THE LOMBARDY DATABASE

