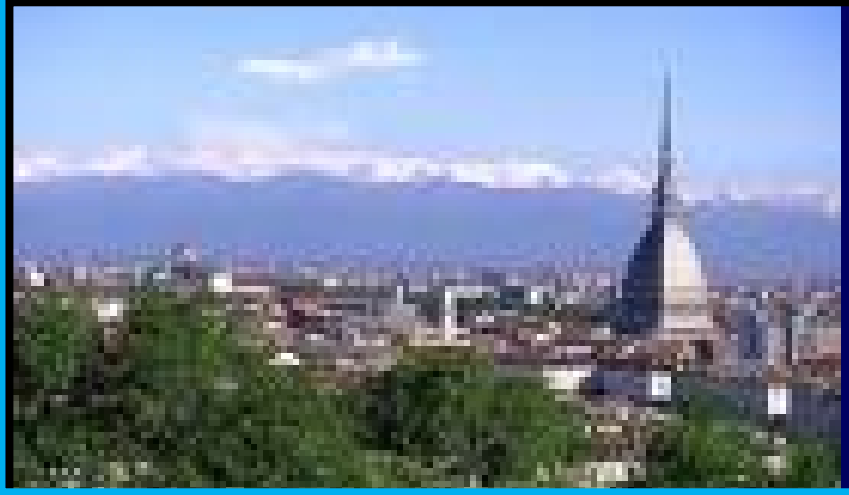


5th JMC - Joint Meeting with Mayo Clinic

Turin
15-16 October 2009

Rationale for combination and high dose therapy
New opportunities for sartans

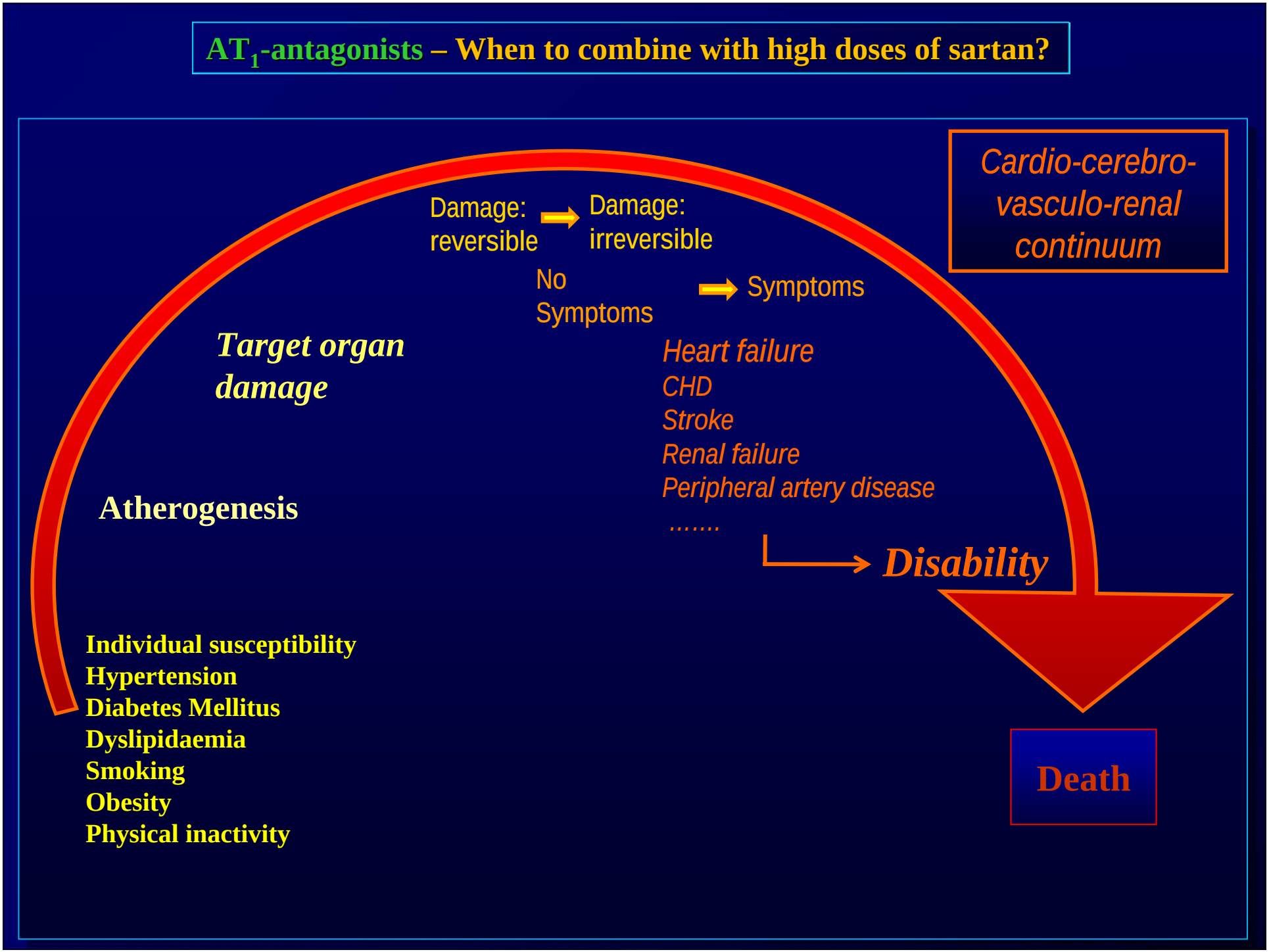
Claudio Ferri

Università di L'Aquila

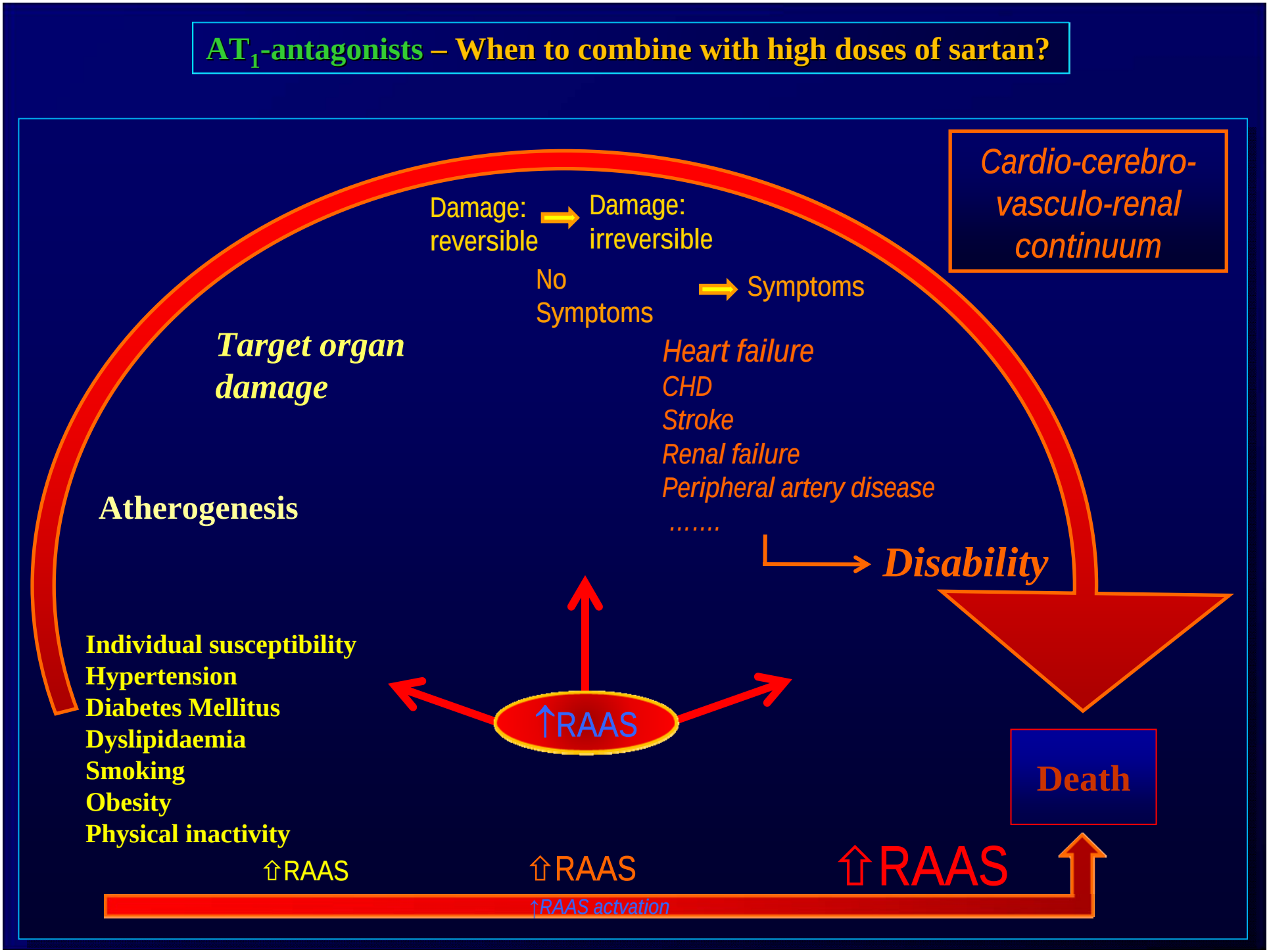
Facoltà di Medicina e Chirurgia

Dipartimento di Medicina Interna e Sanità Pubblica

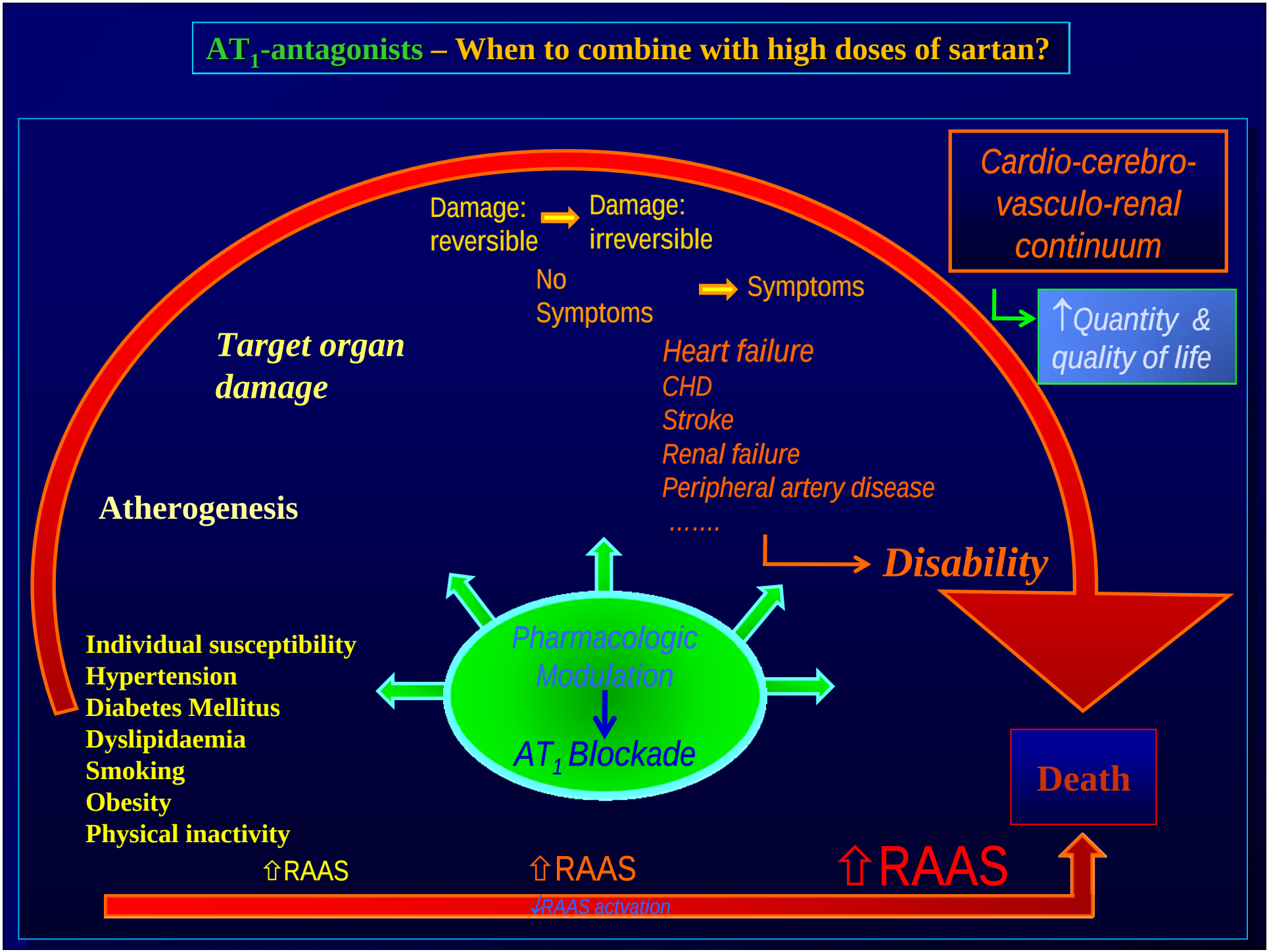
AT_1-antagonists – When to combine with high doses of sartan?



AT_1-antagonists – When to combine with high doses of sartan?

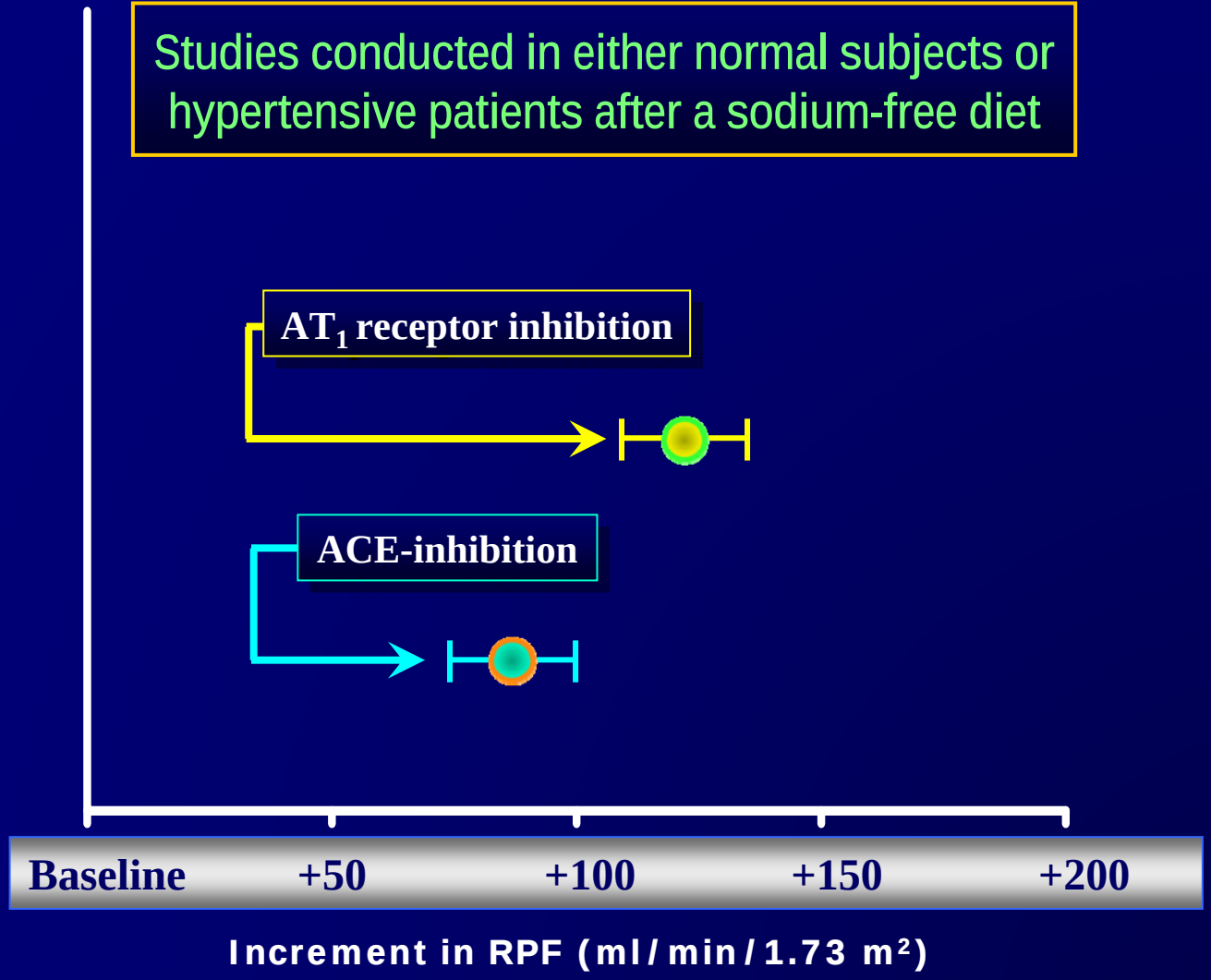


AT_1-antagonists – When to combine with high doses of sartan?



Changes in renal plasma flow (RPF) after RAAS inhibition

Studies conducted in either normal subjects or hypertensive patients after a sodium-free diet



Modified from: Hollenberg NK et al. Hypertension. 1998;32(3):387-92. and Ferri C et al. Circulation 1998, 93:105-112

AT_1-antagonists – When to combine with high doses of sartan?

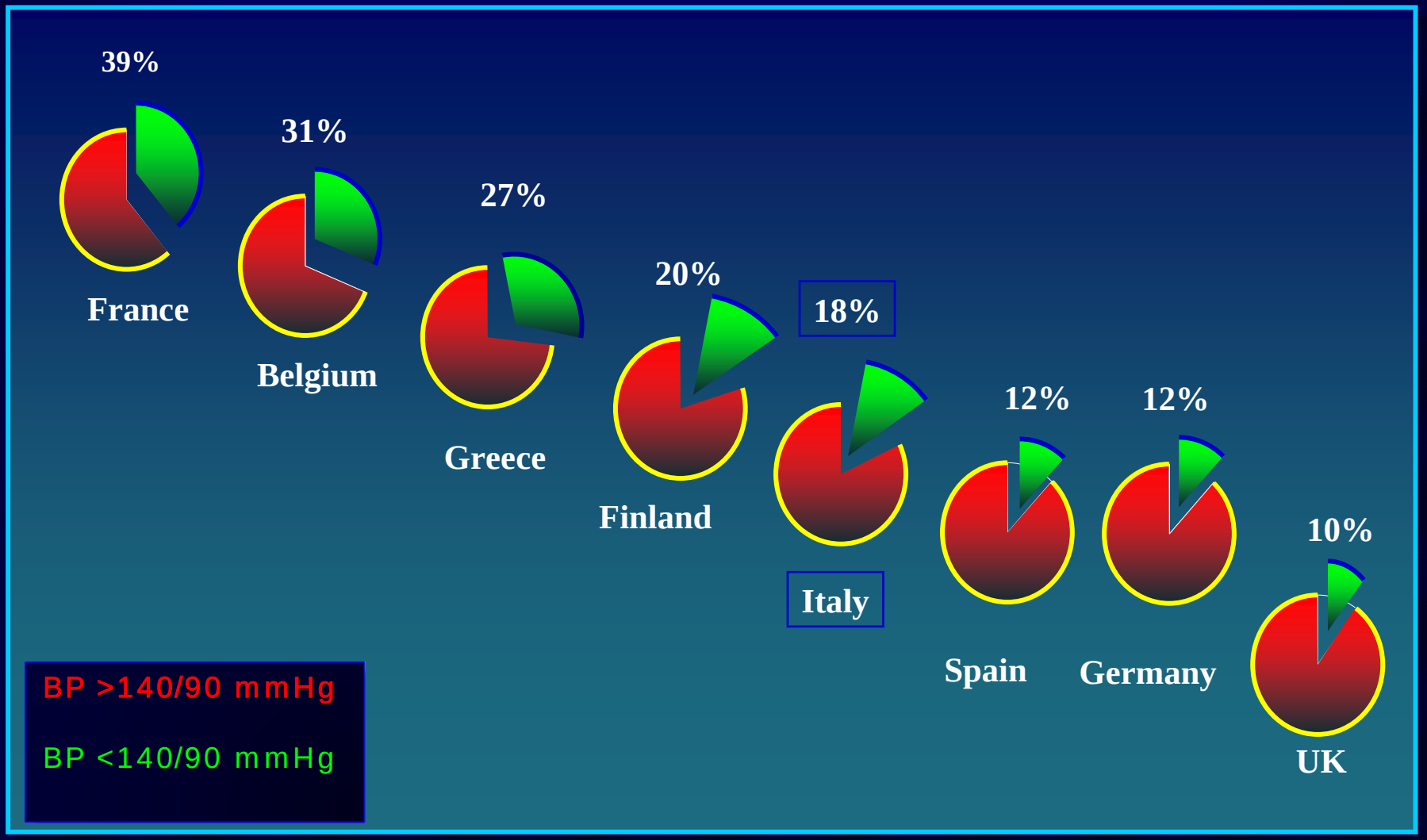
When: an higher antihypertensive efficacy is requested

AT_1-antagonists – When to combine with high doses of sartan?

When: an higher antihypertensive efficacy is requested

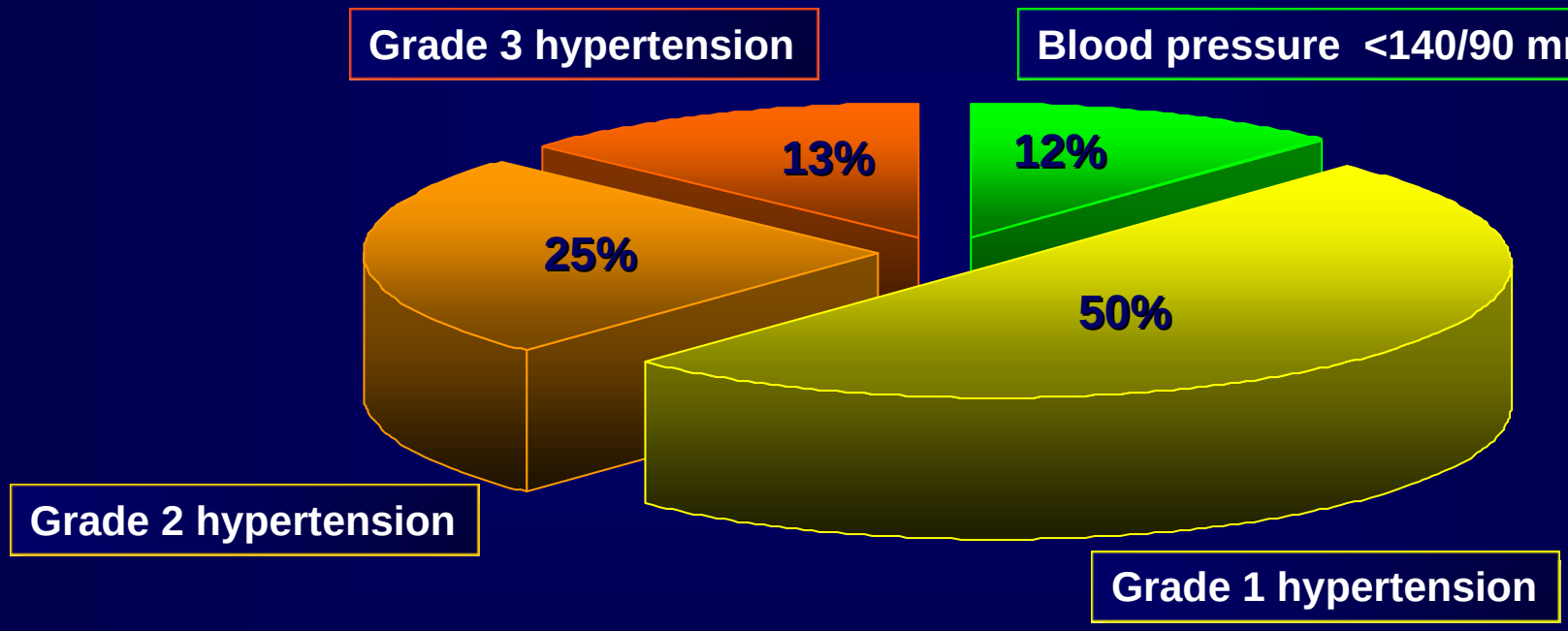
Why should we need an higher antihypertensive efficacy ?

Blood pressure control in Europe



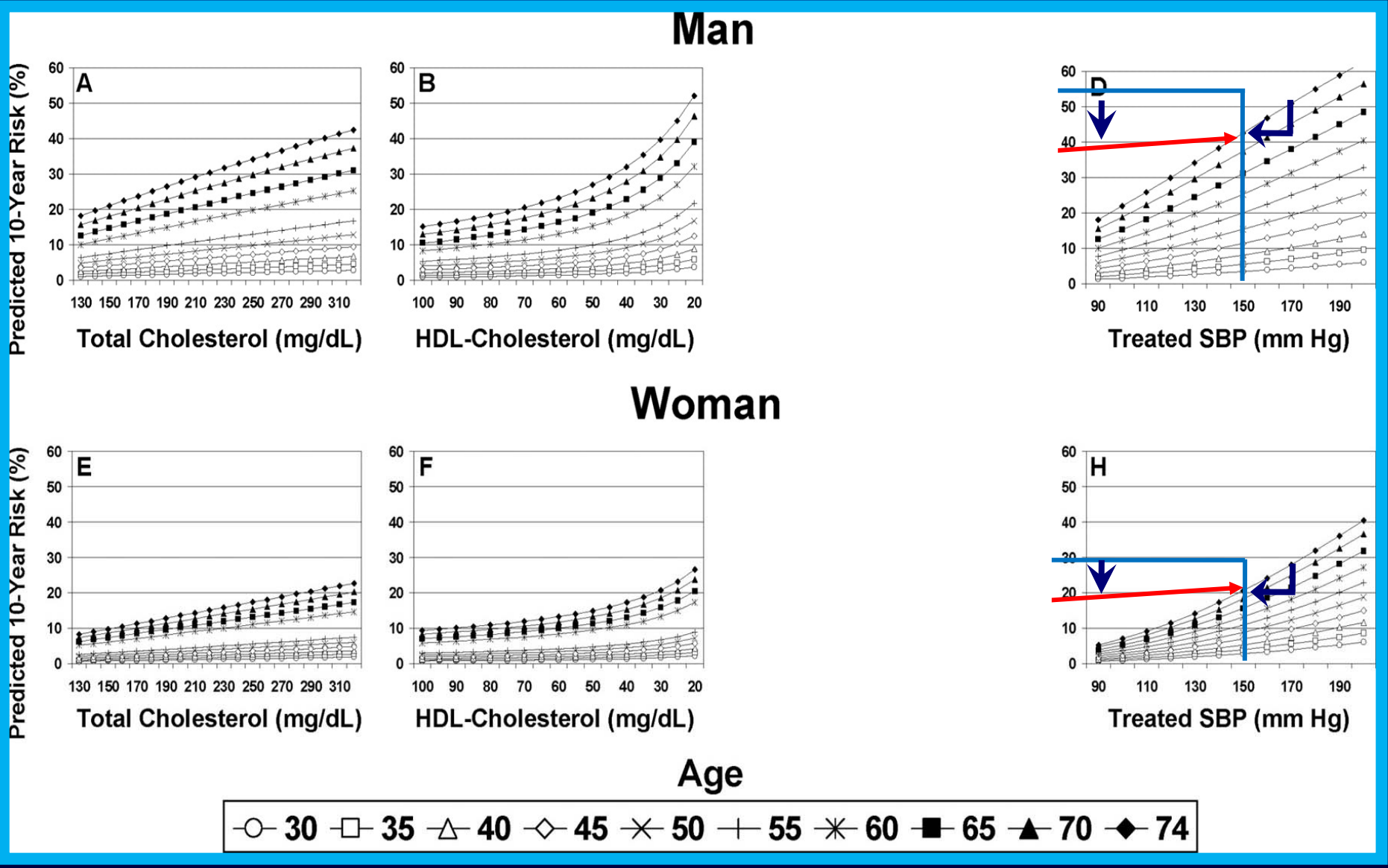
Modified Mancia G et al, J Hypertens 2007

Blood pressure control (treated + untreated) in *Italy*



Ferri C et al, Adv Ther 2008

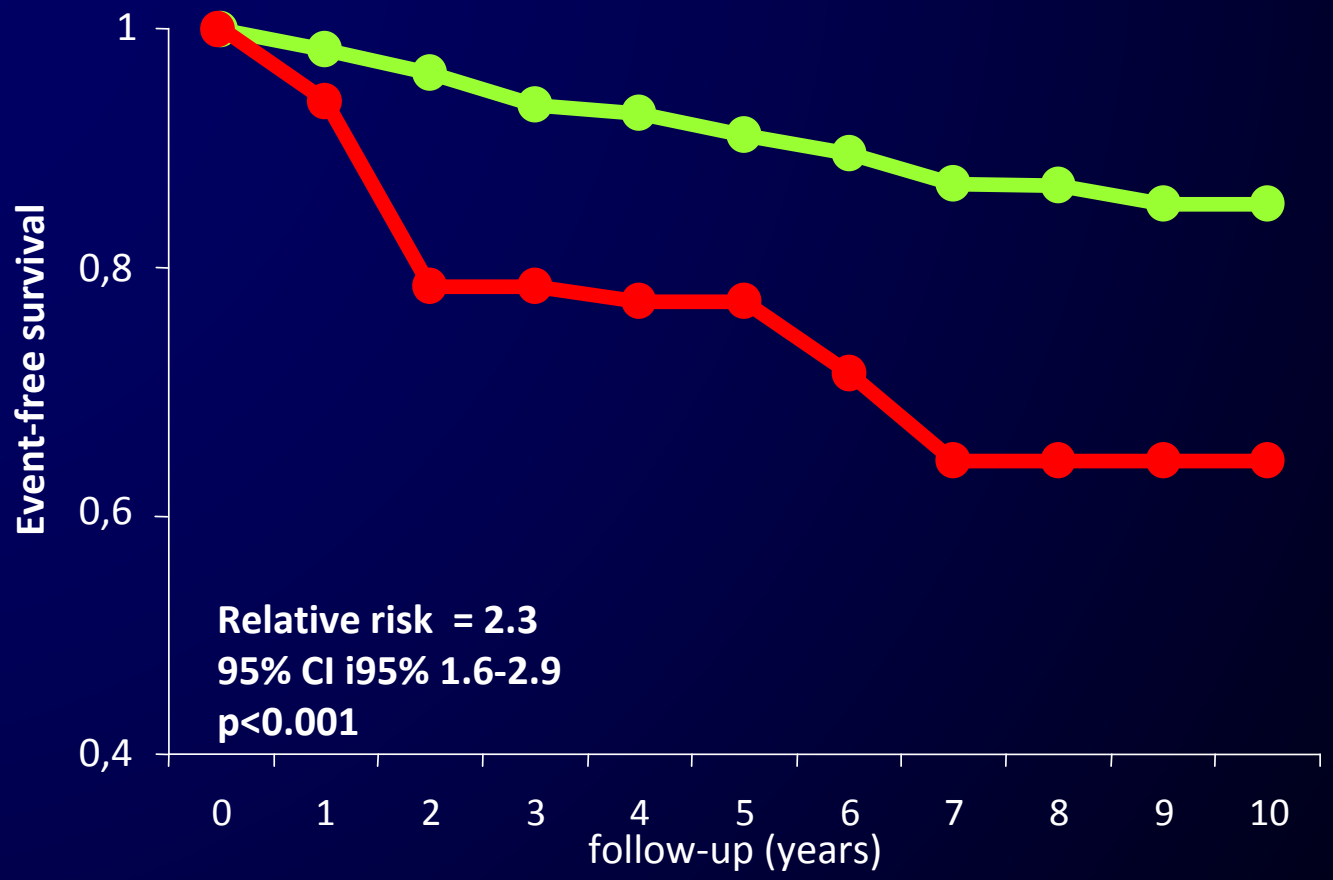
The Framingham Study: **Ten-year predicted risks for CVD by varying levels of single risk factors in a hypothetical man and woman at selected ages, with other risk factors held constant at approximate age-adjusted national means (including nondiabetic, nonsmoking, and no antihypertensive use)**



Marma,A.K. Lloyd-Jones DM. **Circulation 2009;120:384-390**

AT_1-antagonists – When to combine with high doses of sartan?

When: an higher antihypertensive efficacy is requested



Borghi C et al. J Hypertens. 2004 ;22(9):1707-16.

AT_1-antagonists – When to combine and when to use high doses?

When: an higher antihypertensive efficacy is requested

What about the role of higher doses of sartans ?

How to decide between Monotherapy and Combination

Consider:
BP level
Other cardiovascular risk factors
Subclinical organ damage
Overt concomitant diseases
Rapidity to achieve BP goal

- Mild BP increment
- Low or moderate CV risk
- Conventional BP goal

Choose

Monotherapy (low dose)

If BP is uncontrolled

Increment of dose

Change drug

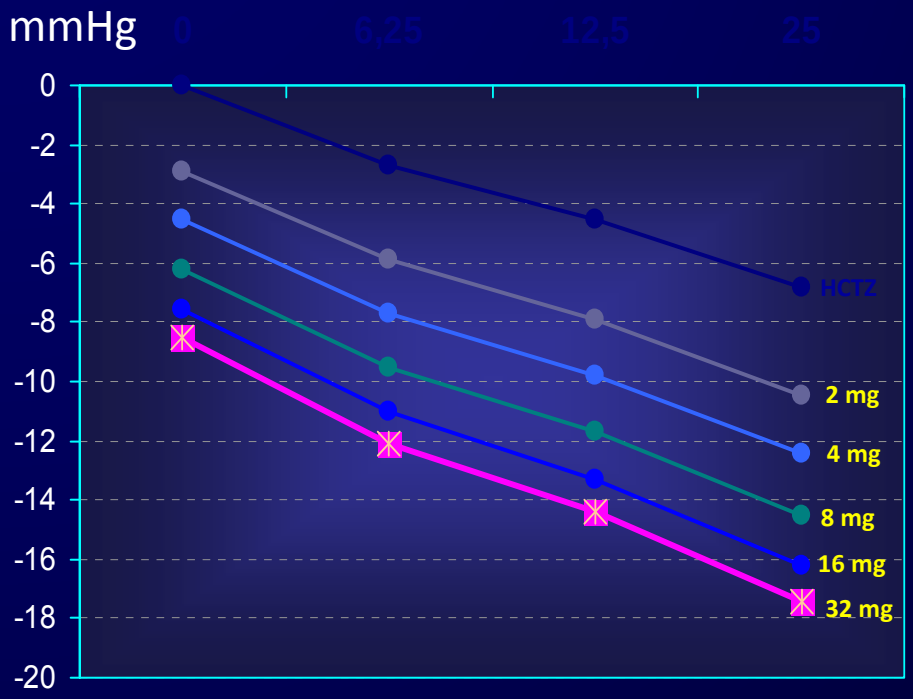
If BP is uncontrolled

Combination therapy

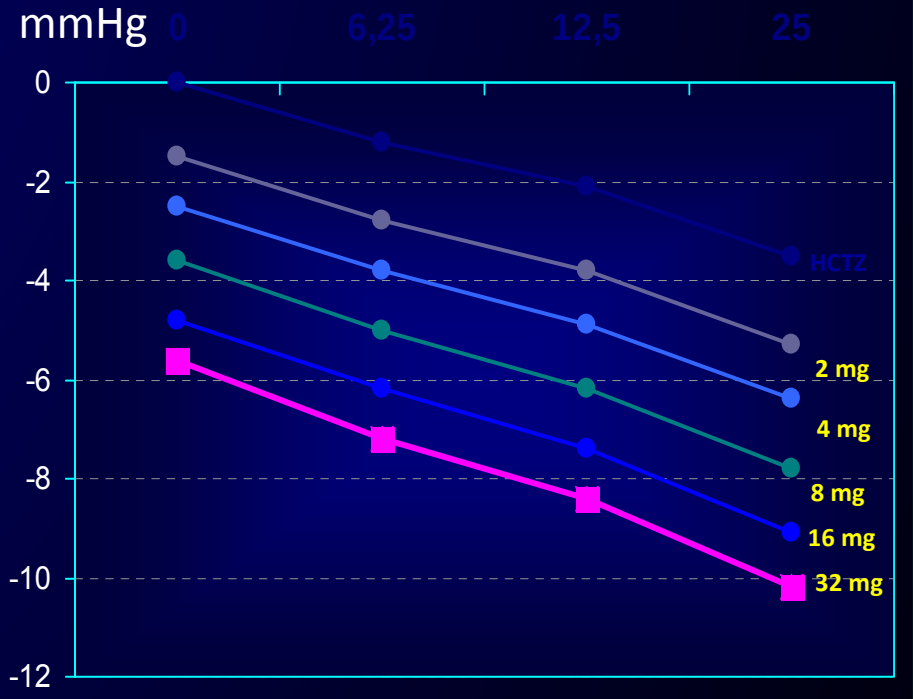
Monotherapy (high dose)

AT_1-antagonists – When to combine with high doses of sartan?

Reduction of SBP with candesartan (from 2 to 32 mg ± HCTZ a dosaggi (meta-analisys 7 studies, n = 4632)



Reduction of DBP with candesartan (from 2 to 32 mg ± HCTZ a dosaggi (meta-analisys 7 studies, n = 4632)



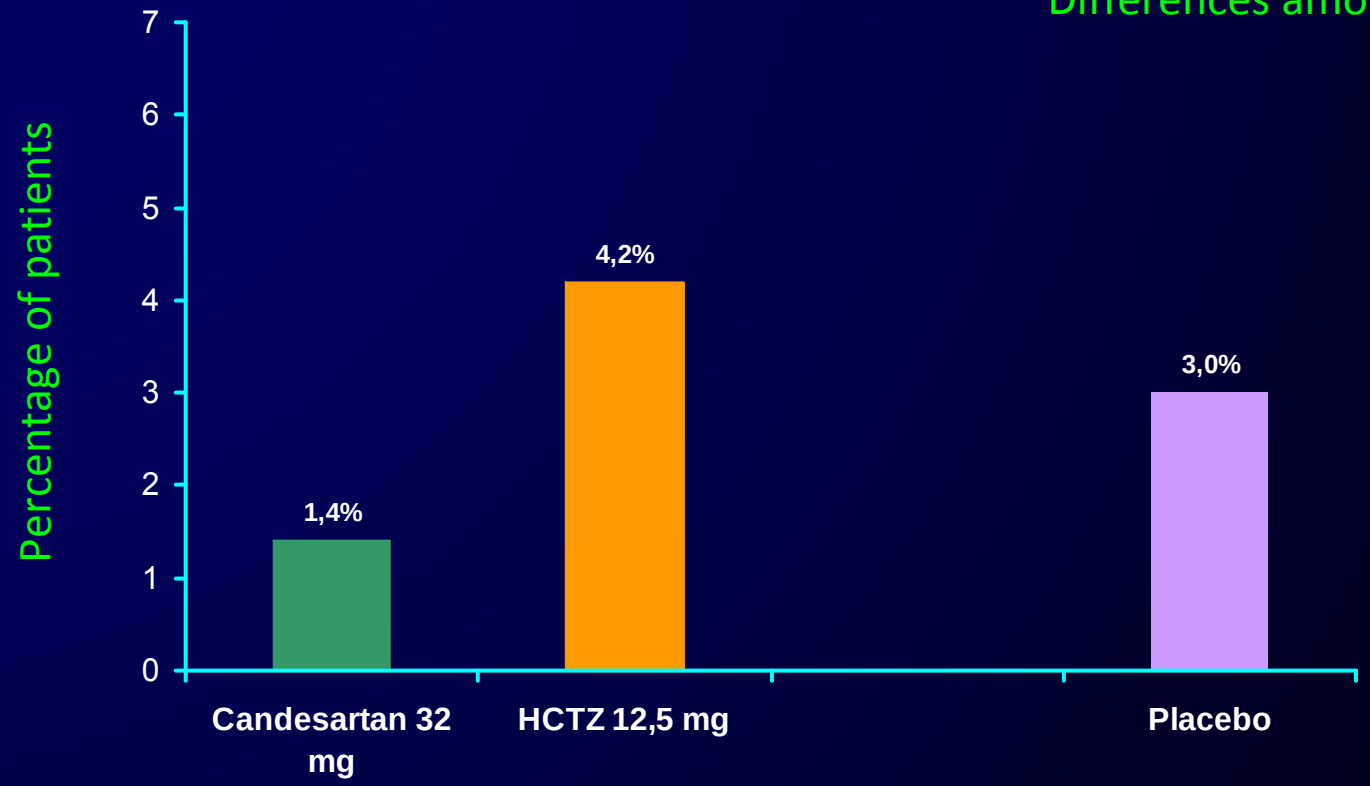
HCTZ: Hydrochlorothiazide

Karlson BW, et al. A dose-response analysis of candesartan-hydrochlorothiazide combination therapy in patients with hypertension. Blood Press. 2009 May 22;1-8 [epub]

AT_1-antagonists – When to combine with high doses of sartan?

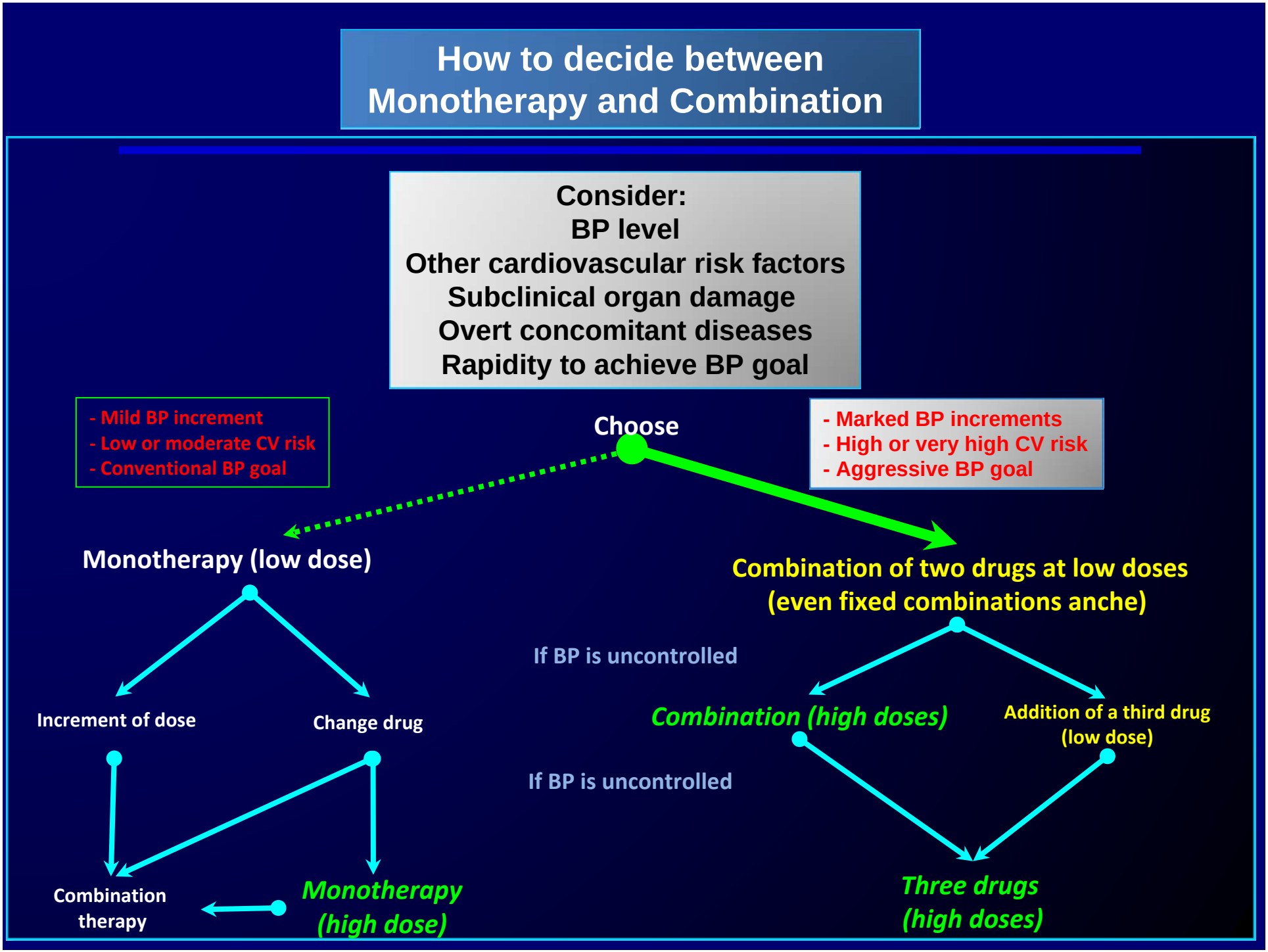
Adverse events leading to interruption of therapy

Differences among groups: NS



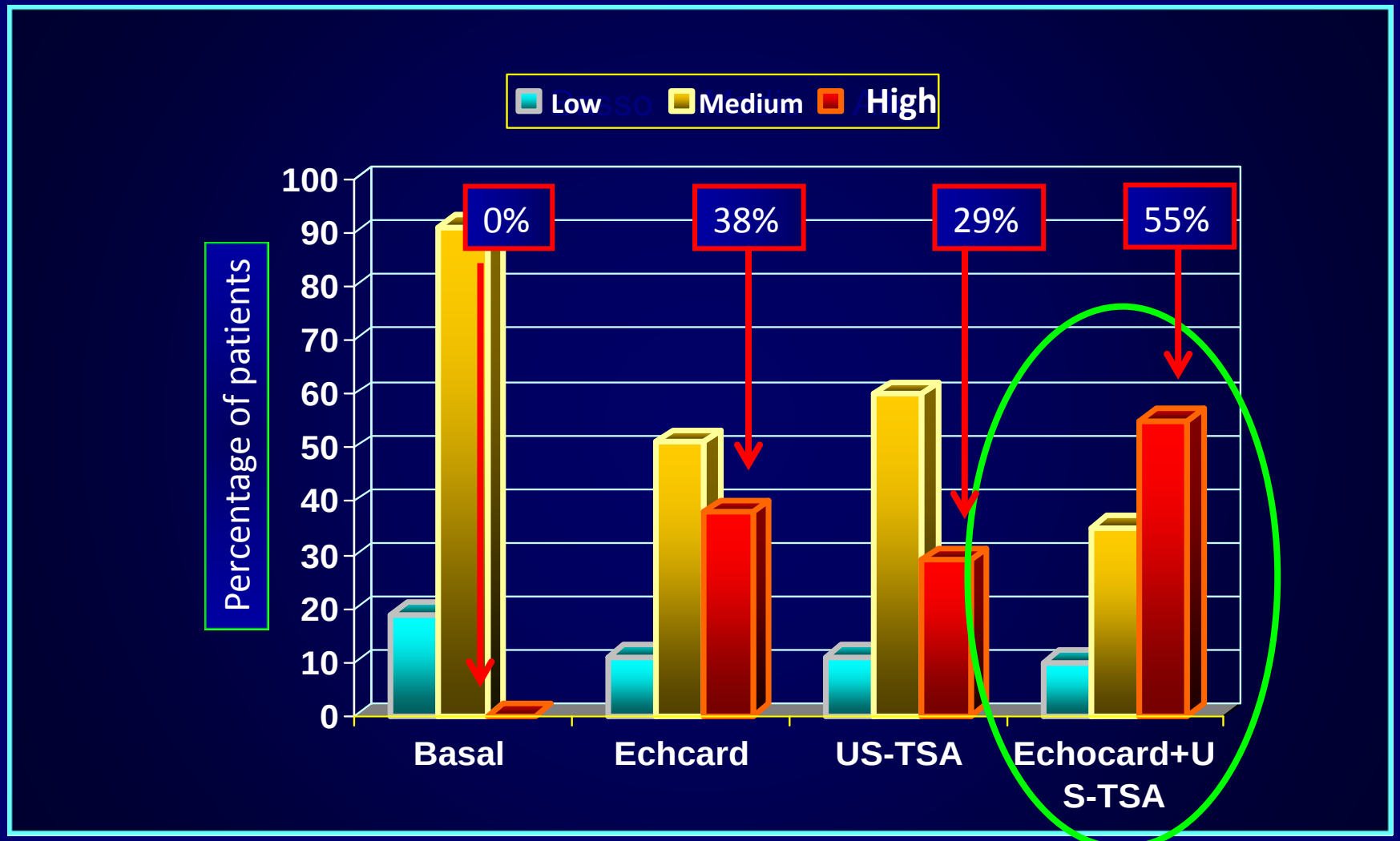
Papademetriou V, et al. Combination therapy with candesartan cilexetil and hydrochlorothiazide in patients with systemic hypertension. J Clin Hypertens. 2000;2:372-8.

How to decide between Monotherapy and Combination



Role of echocardiography and carotid ultrasonography in stratifying risk in patients with essential hypertension: the Assessment of Prognostic Risk Observational Survey (APROS).

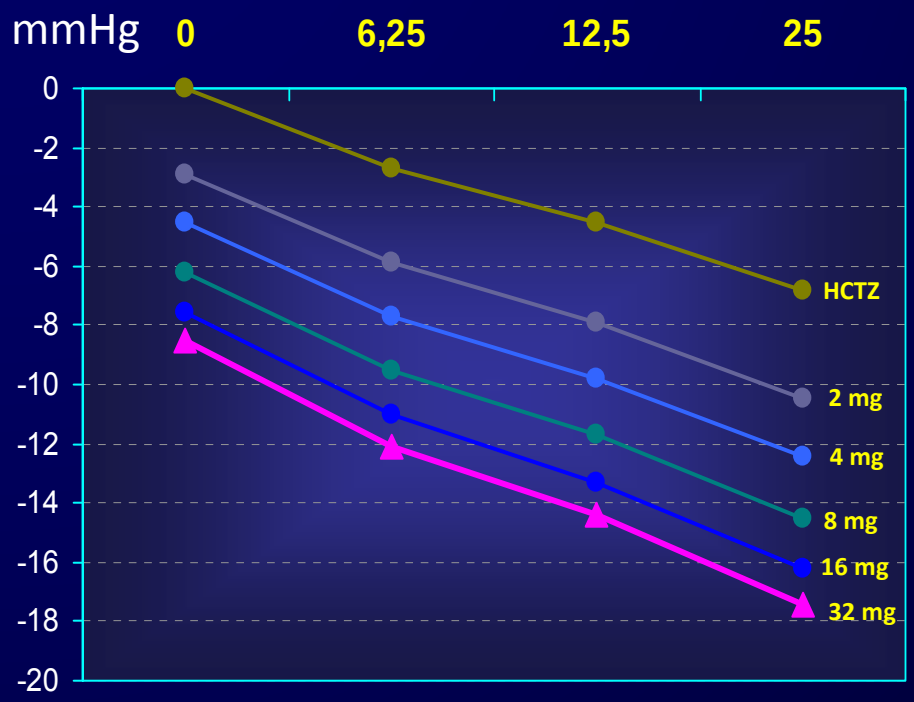
Data from 1.074 consecutive untreated hypertensive outpatients



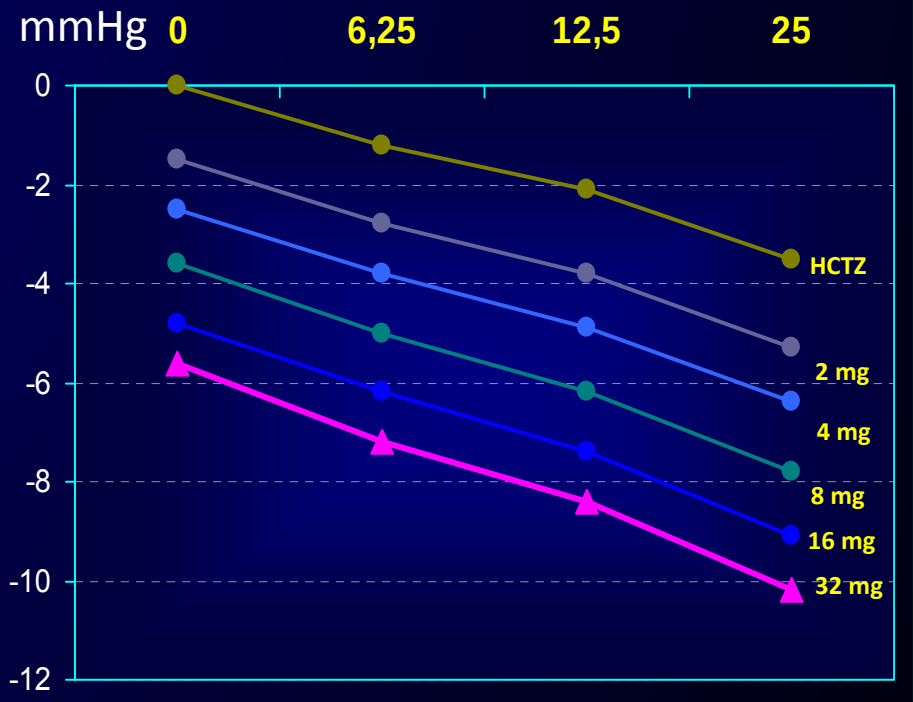
Cuspidi et Al, J Hypertens 2002,;20(7):1307-14

AT_1-antagonists – When to combine and when to use high doses?

Reduction of SBP with candesartan (2 - 32 mg) ± HCTZ a dosaggi variabili (meta-analysis 7 studies, n = 4632)



Reduction of DBP with candesartan (2 - 32 mg) ± HCTZ a dosaggi variabili (meta-analysis 7 studies, n = 4632)

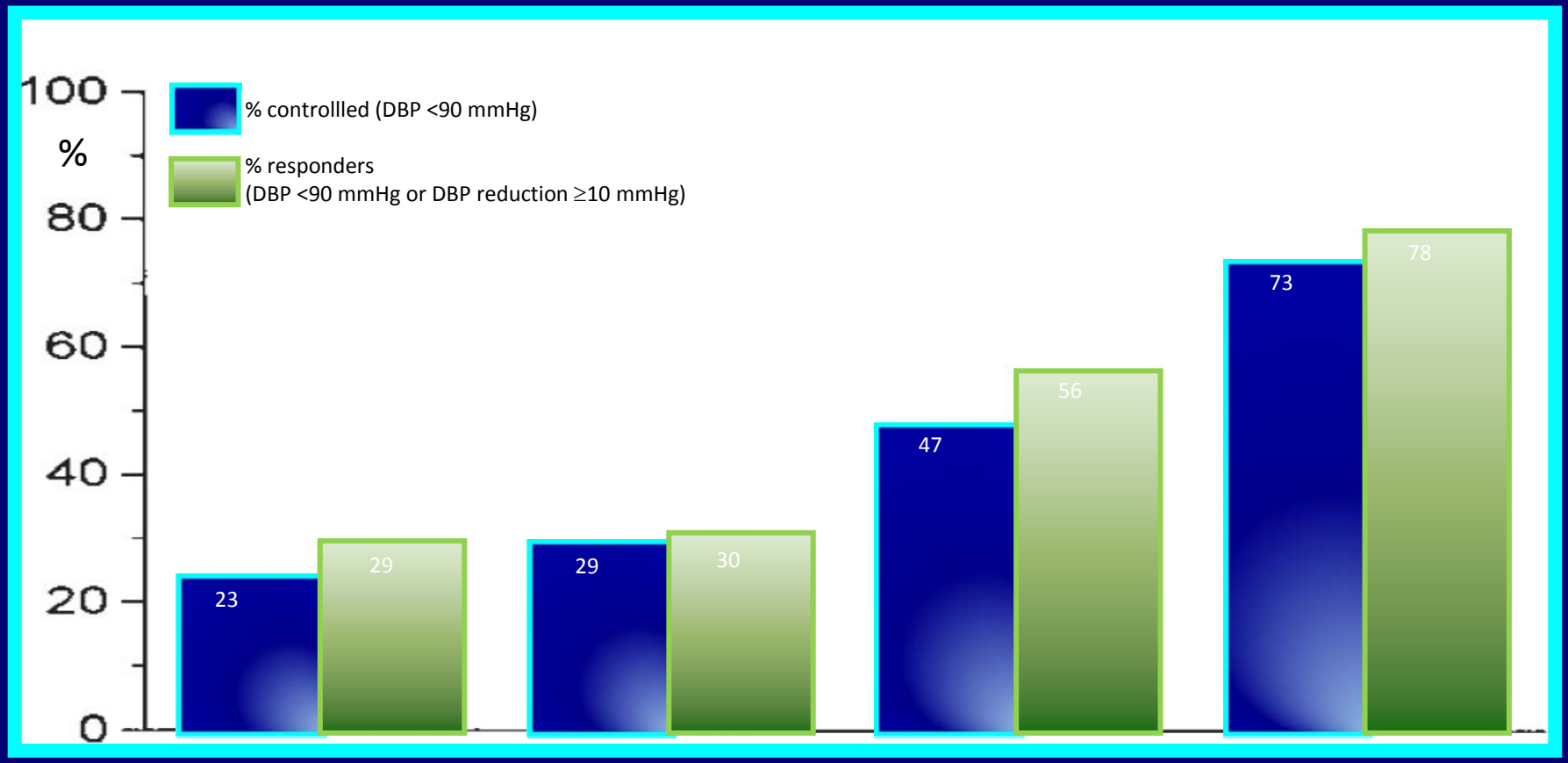


HCTZ: hydrochlorothiazide

Karlson BW, et al. A dose-response analysis of candesartan-hydrochlorothiazide combination therapy in patients with hypertension. Blood Press. 2009 May 22;1-8 [epub]

AT_1-antagonists – When to combine with high doses of sartan?

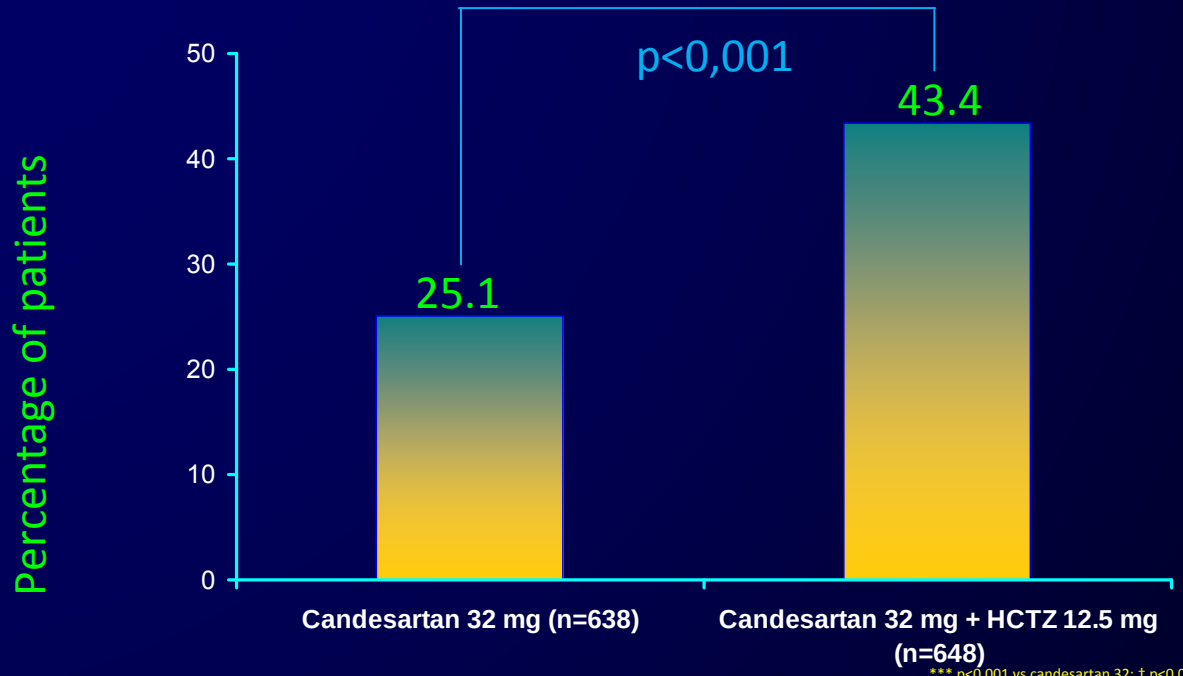
Percentage of patients *responders* e in good BP control



Papademetriou V, et al. Combination therapy with candesartan cilexetil and hydrochlorothiazide in patients with systemic hypertension. J Clin Hypertens. 2000;2:372-8.

AT_1-antagonists – When to combine with high doses of sartan?

Antihypertensive Efficacy: patients in *good BP control* (SBP <140 mmHg; DBP <90 mmHg)



*** p<0,001 vs candesartan 32; † p<0,05 vs candesartan/HCT 32/12,5 mg

Patients% (95% IC)	Candesartan 32 mg(n=638)	Candesartan/HCTZ 32/12,5 mg (n=648)	Candesartan/HCTZ 32/25 mg (n=659)
Control SBP and DBP (<140/<90 mmHg)	25,1 (21,7–28,4)	43,4*** (39,5–47,2)	48,9*** (45,0–52,7)
Control DBP (<90 mmHg)	42,3 (38,5–46,2)	59,4*** (55,6–63,2)	63,4*** (59,8–67,1)
Responders (DBP<90 mmHg or red DBP ≥10 mmHg)	46,6 (42,7–50,4)	65,4*** (61,8–69,1)	71,2***† (67,7–74,6)

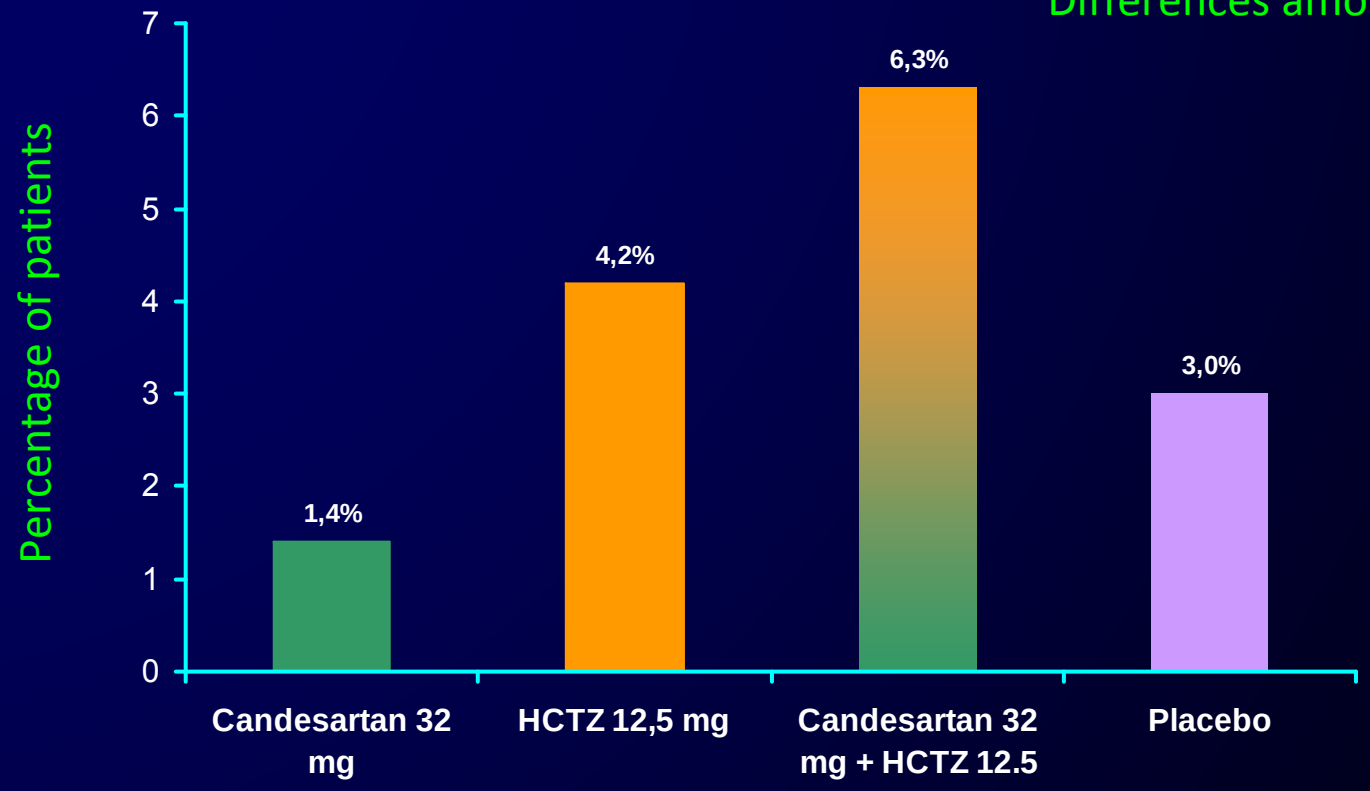
HCTZ: hydrochlorothiazide

Bönner G, for the Multicentre Study Group. Antihypertensive efficacy and tolerability of candesartan-hydrochlorothiazide 32/12.5 mg and 32/25 mg in patients not optimally controlled with candesartan monotherapy. Blood Press. 2008;17(Suppl.2):22-30.

AT_1-antagonists – When to combine with high doses of sartan?

Adverse events leading to interruption of therapy

Differences among groups: NS



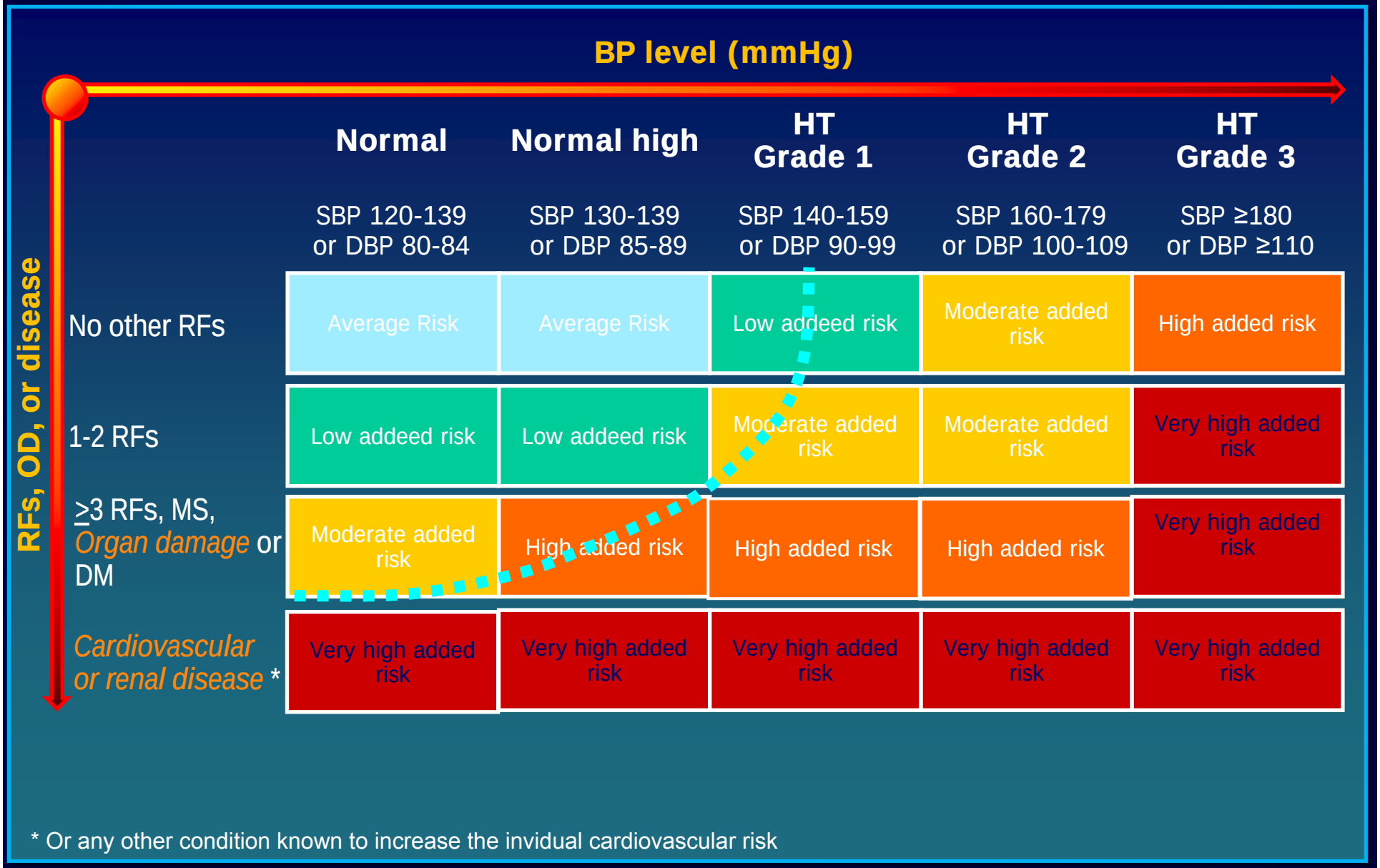
Papademetriou V, et al. Combination therapy with candesartan cilexetil and hydrochlorothiazide in patients with systemic hypertension. J Clin Hypertens. 2000;2:372-8.

AT_1-antagonists – When to combine with high doses of sartan?

When: *an higher organ protection is required*

What about the role of higher doses ?

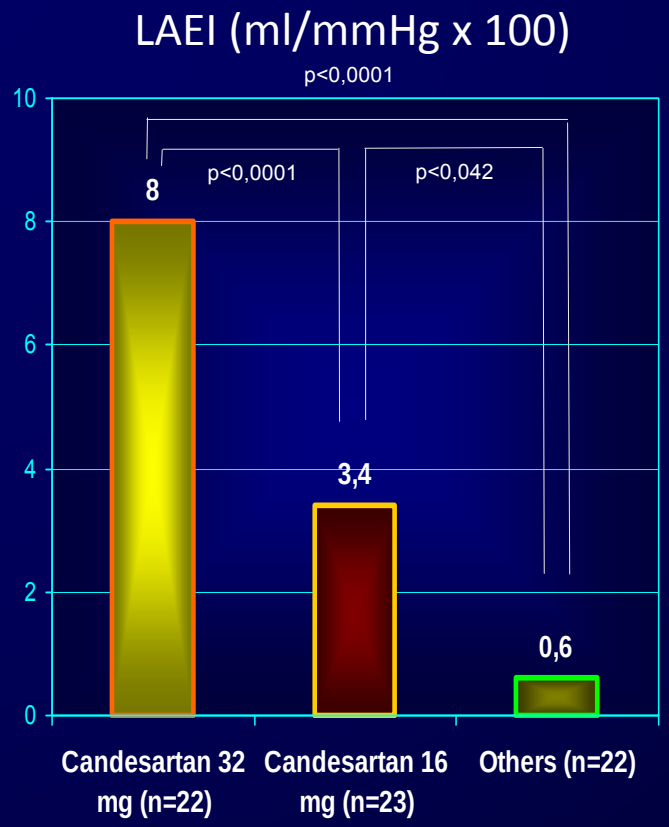
Global cardiovascular risk
RISK STRATIFICATION



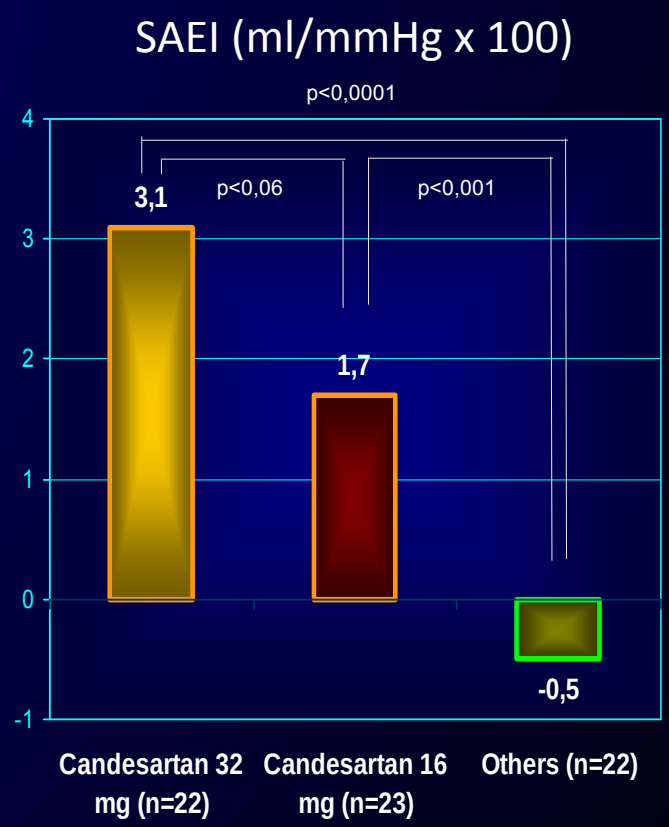
* Or any other condition known to increase the invidual cardiovascular risk

AT_1-antagonists – When to combine with high doses of sartan?

Changes in large artery distensibility
(baseline vs end of therapy [6 months])



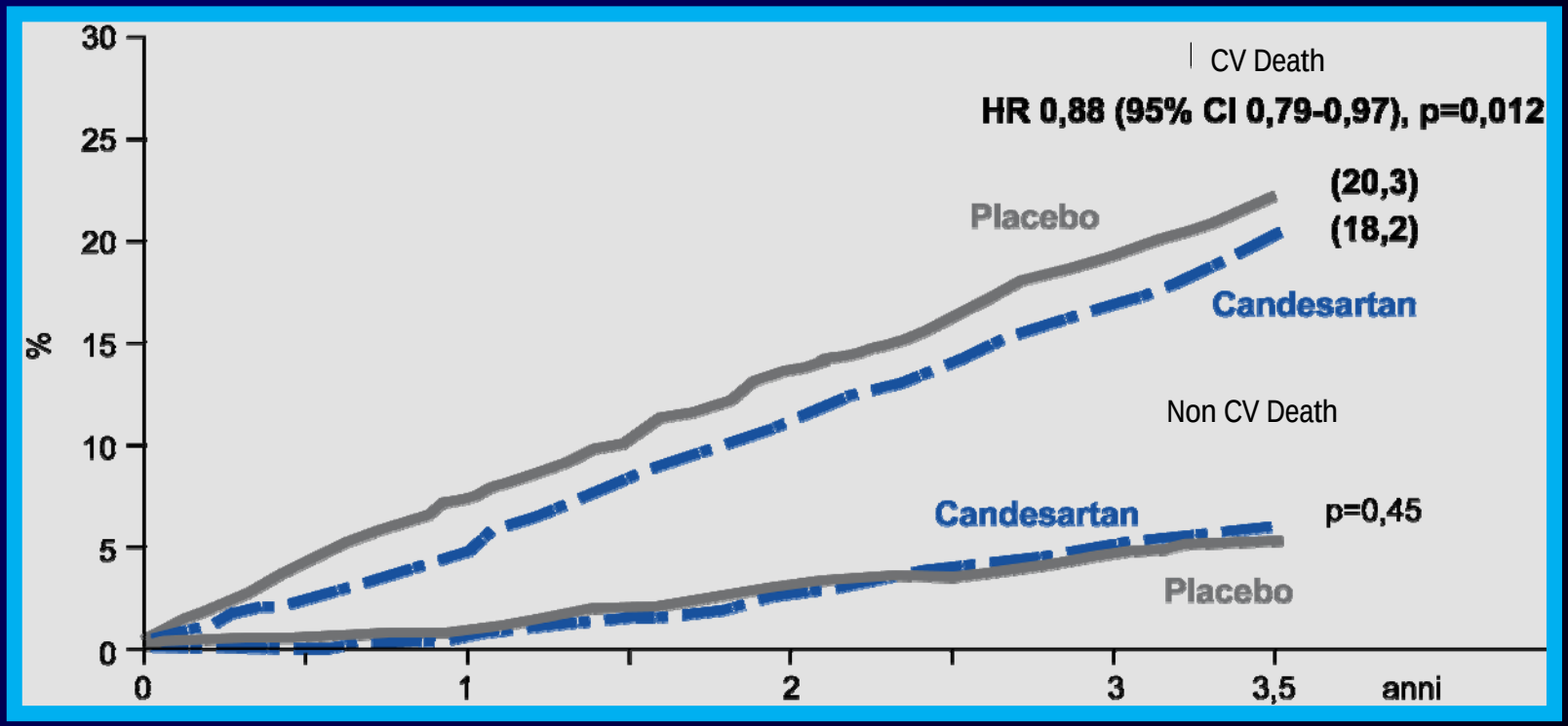
Changes in small artery distensibility
(baseline vs end of therapy [6 months])



Shargorodsky M, et al. High dose treatment with angiotensin II receptor blocker in patients with hypertension: differential effect of tissue protection versus blood pressure lowering. Atherosclerosis. 2008;197:303-10.

AT_1-antagonists – When to combine with high doses of sartan?

CHARM Overall: cardiovascular and non cardiovascular mortality



Pfeffer MA, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet. 2003;362:759-66.

AT_1-antagonists – When to combine with high doses of sartan?

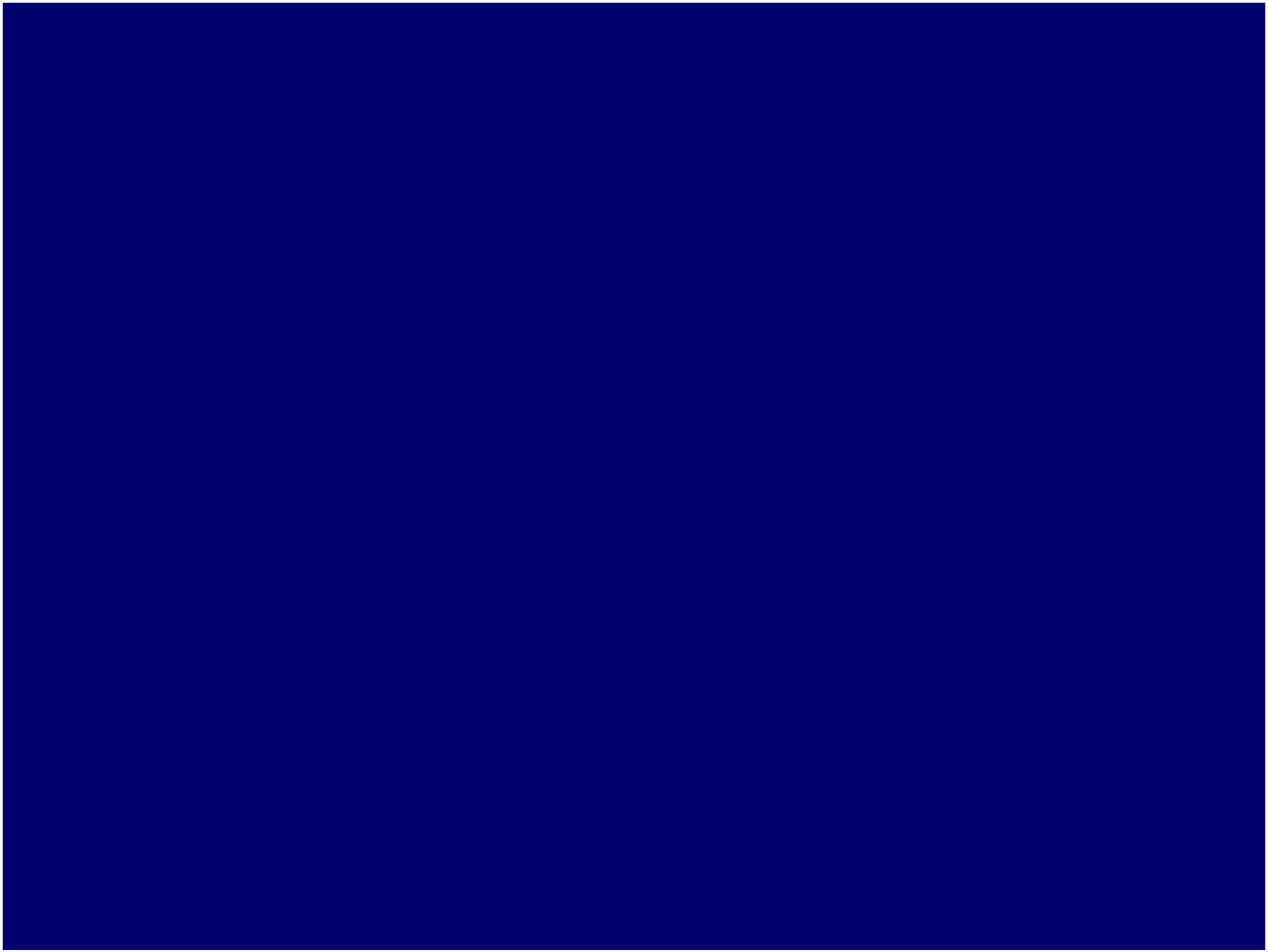
When you need:

An higher anitihypertensive efficacy

An higher organ protection

Excellent tolerability

AT_1-antagonists – When to combine with the right, individualized dose of sartan



Friday 16thOctober 2009 (09:00—18:30PM)
SESSION VII (16:40— 18:00)
Organizational and treatment advances in cardiology
Chairmen: S. Marra, M. Bell
Adherence to treatment guidelines for nstemi:
the role of a network between hospitals (A. Manari)
Anti-aggregation therapy: when it is not effective
(M. Valgimigli)
Smoking cessation treatment: an issue for cardiologist?
(P. Clavario)
Thrombus aspiration in acute myocardial infarction
(F. Varbella)
Program GREAT INNOVATIONS IN CARDIOLOGY
> **Friday 16thOctober 2009 (09:00—18:30PM)**
Pharmacological treatment of atrial fibrillation: current
status and future prospects (D. Caponi)
Non Invasive Cardiac Angiogenesis Therapy
with schock-wave) (G. Alunni)
Rationale for combination and high-dose therapies:
new opportunities with sartans (C. Ferri)
18:00 Discussion and questions
CME verifying