ΑΠΟΚΛΕΙΣΜΟΣ ΤΟΥ ΣΥΣΤΗΜΑΤΟΣ ΡΕΝΙΝΗΣ: ΝΕΑ ΠΡΟΣΕΓΓΙΣΗ

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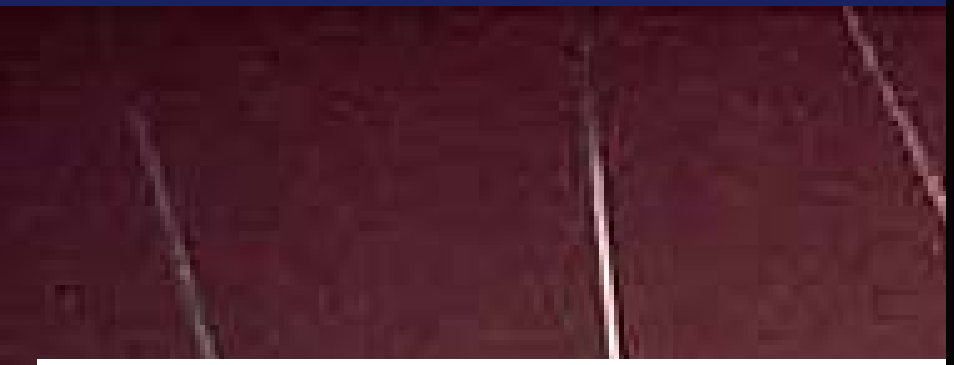
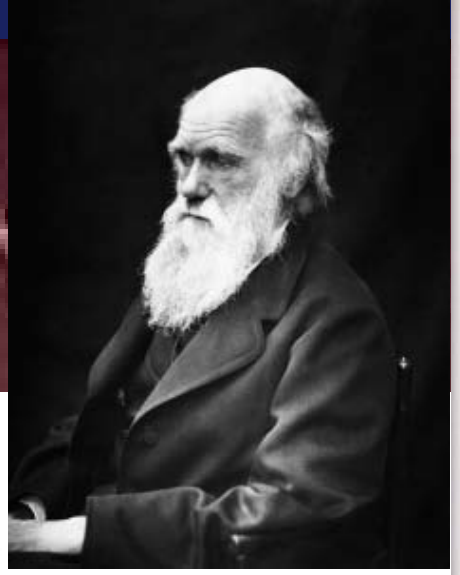
Αναπληρωτής Καθηγητής Νεφρολογίας

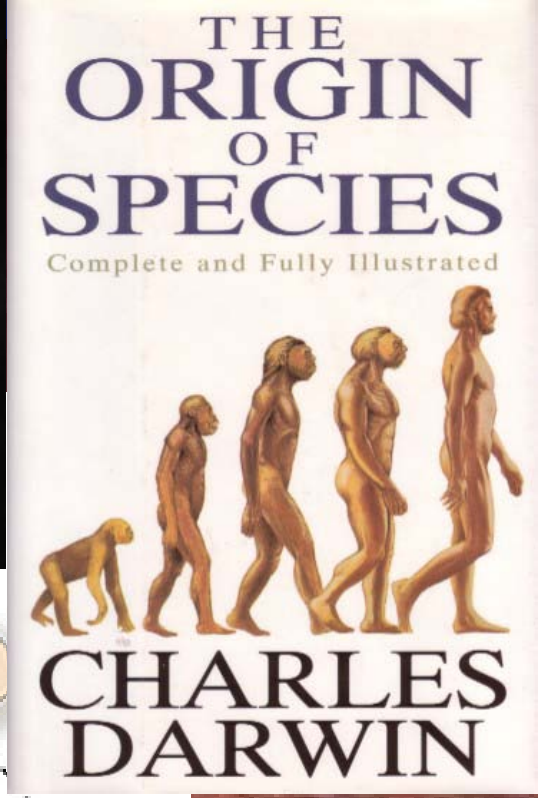
Υπεύθυνος Νεφρολογικής Μονάδας

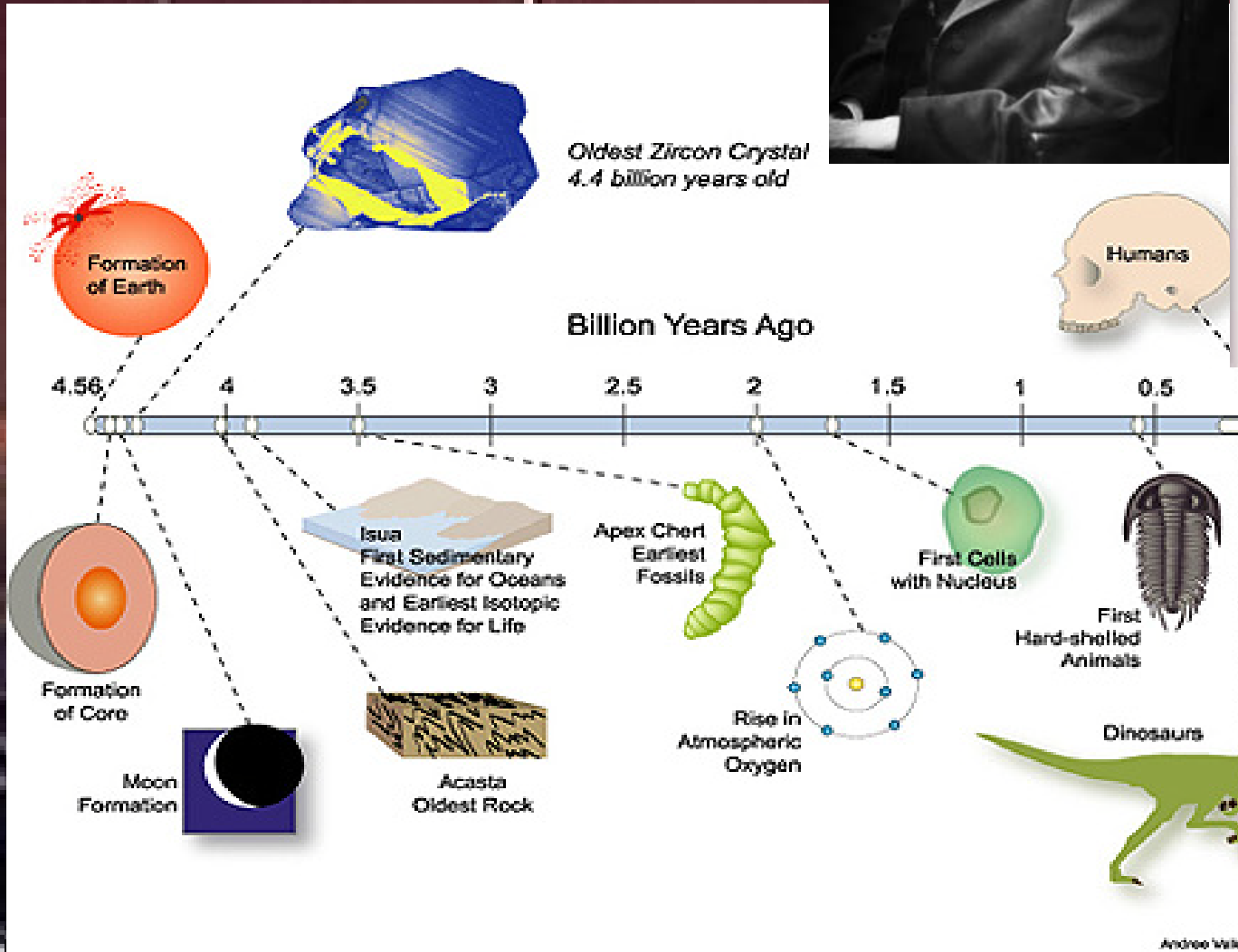
Β΄ Προπαιδευτική Παθολογική Κλινική

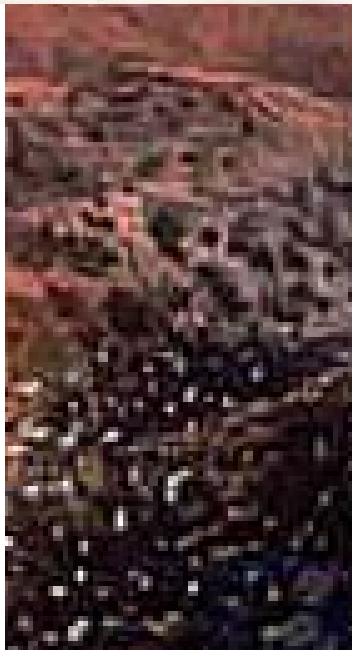
Πανεπιστημιακό Γ.Ν. «ΑΤΤΙΚΟΝ»

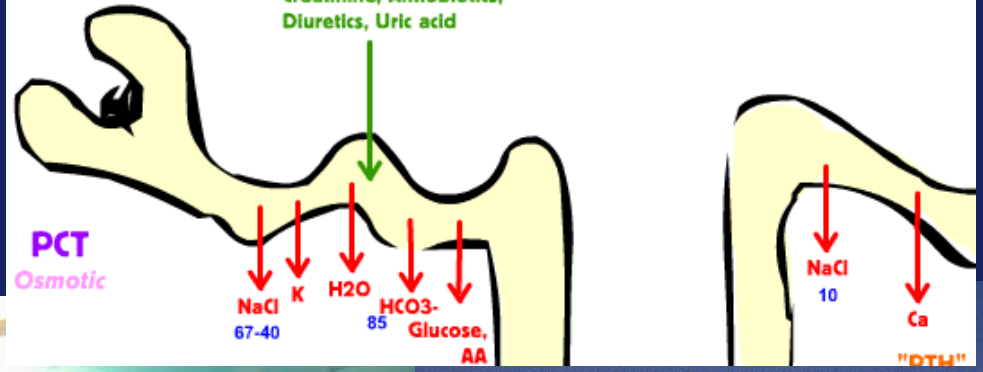


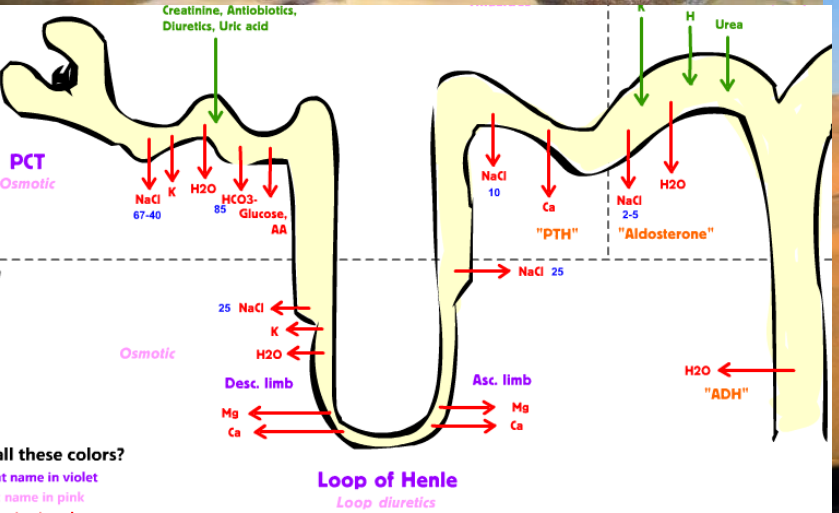



THE
ORIGIN
OF
SPECIES
Complete and Fully Illustrated
CHARLES
DARWIN


Oldest Zircon Crystal
4.4 billion years old
Formation of Earth
Humans
Billion Years Ago
4.56
4
3.5
3
2.5
2
1.5
1
0.5
0
Isua
First Sedimentary Evidence for Oceans and Earliest Isotopic Evidence for Life
Apex Chert
Earliest Fossils
First Cells with Nucleus
First Hard-shelled Animals
Formation of Core
Moon Formation
Acasta
Oldest Rock
Rise in Atmospheric Oxygen
Dinosaurs
Andrew Alden

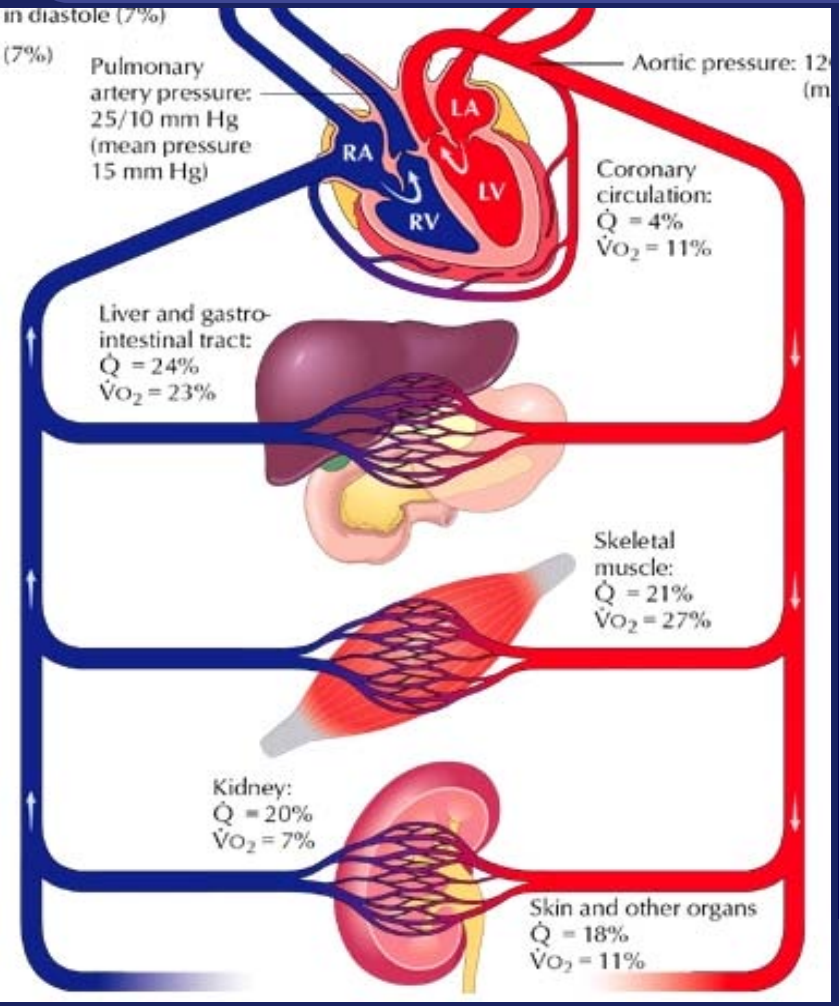






ll these colors?
t name in violet
name in pink

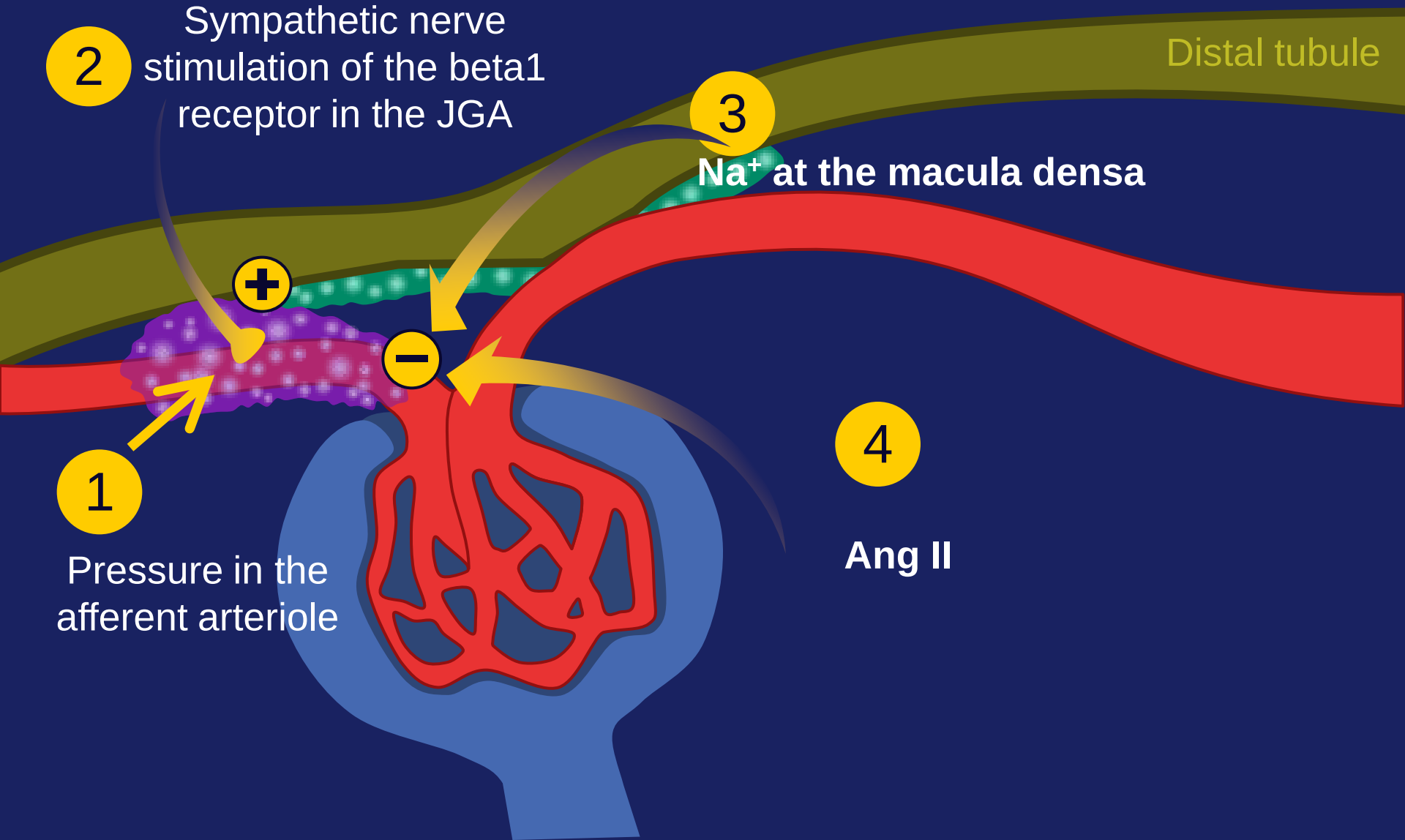
EFFECTIVE VOLUME



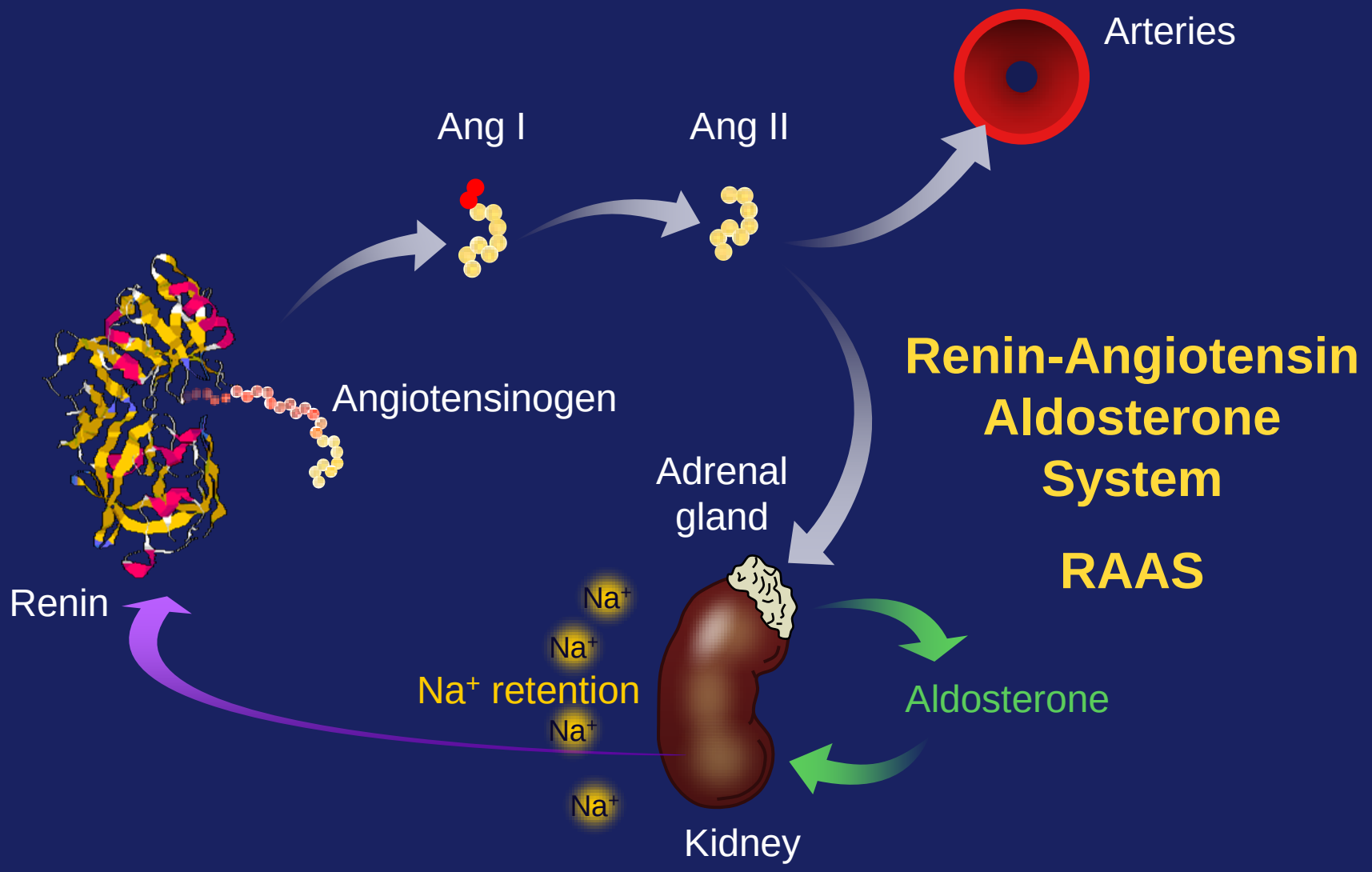
BODY FLUID DISTRIBUTION

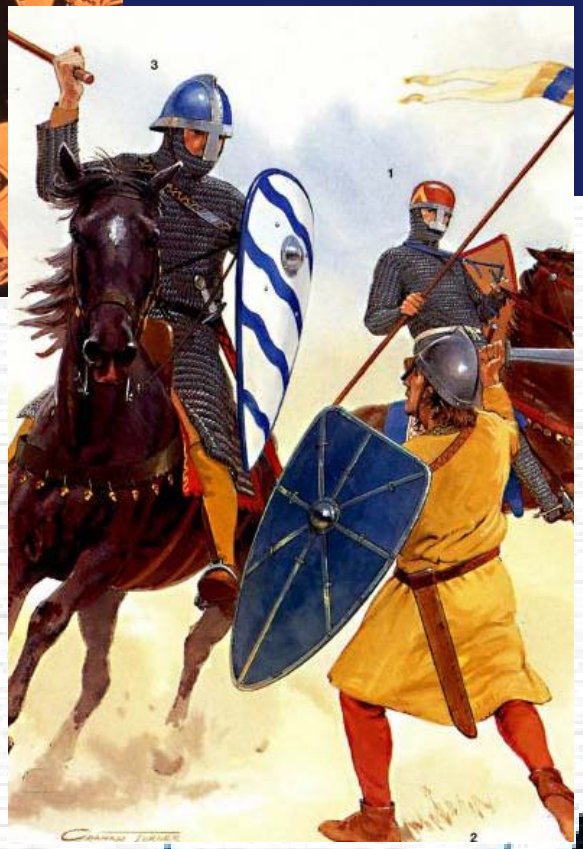
COMPARTMENT	AMOUNT	VOLUME IN 70 KG MAN
Total Body Fluid	60% of Body Weight	42.0 liters
Intracellular Fluid	40% of Body Weight	28.0 liters
Extracellular Fluid (ECF)	20% of Body Weight	14.0 liters
Interstitial Fluid	Two-thirds of ECF	9.4 liters
Plasma Fluid	One-third of ECF	4.6 liters
Venous Fluid	85% of Plasma Fluid	3.9 liters
Arterial Fluid	15% of Plasma Fluid	0.7 liters

Renin secretion is regulated by 4 mechanisms

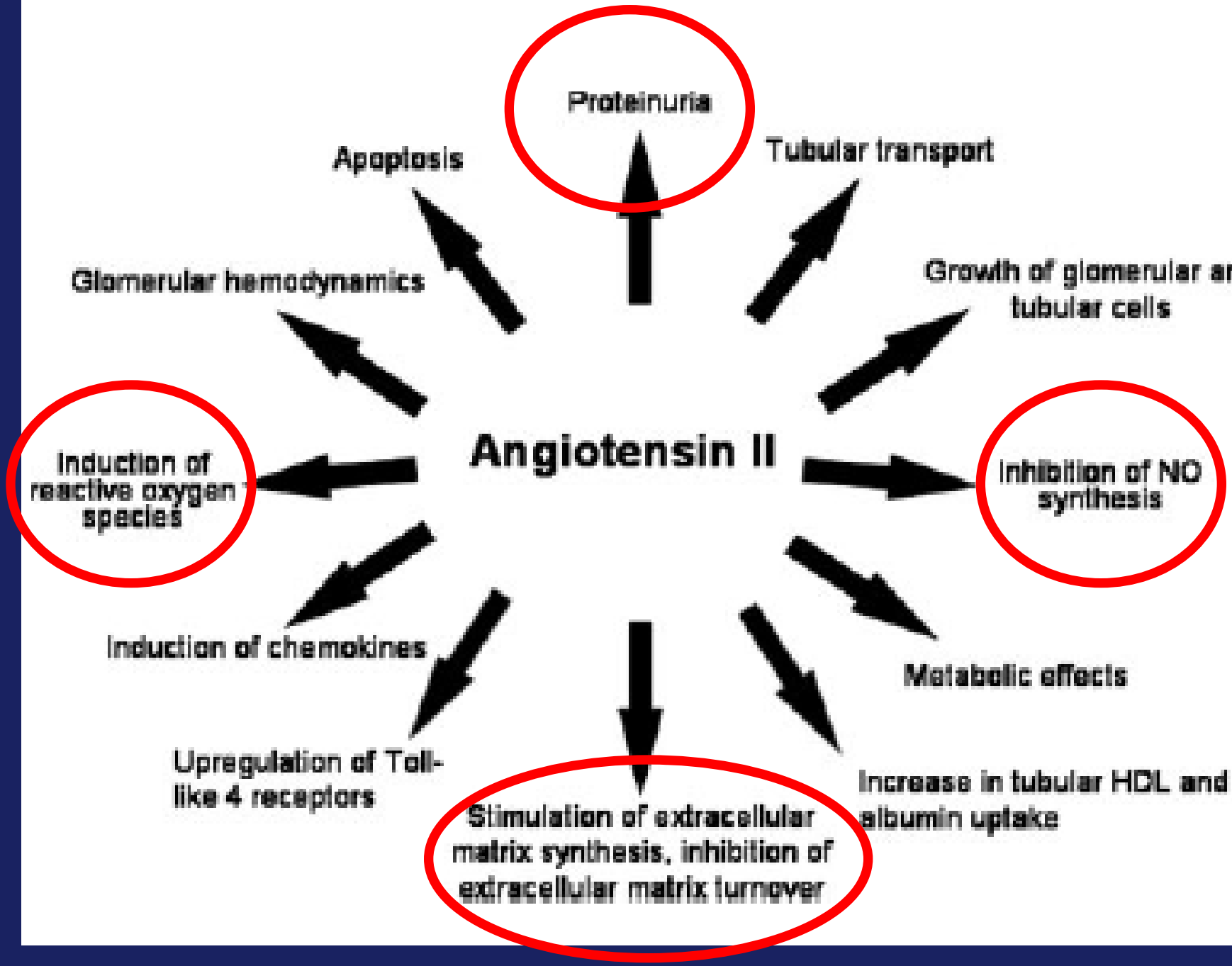


BP = CO X SVR

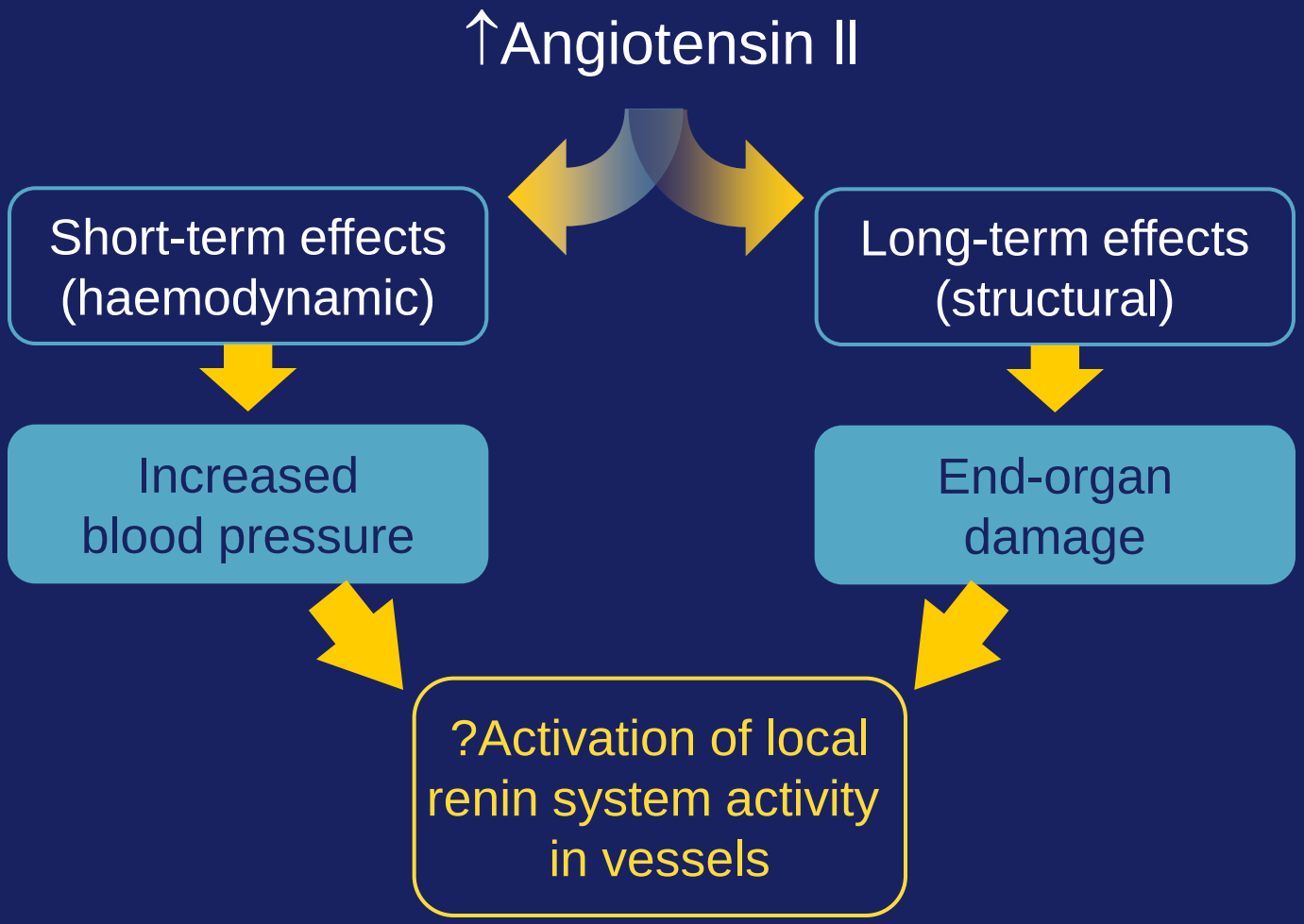

Arteries
Ang I
Ang II
Angiotensinogen
Renin
Adrenal gland
Renin-Angiotensin Aldosterone System
RAAS
Na+
Na+
Na+ retention
Na+
Na+
Aldosterone
Kidney



Life expectancy (years)
80
69
58
47
36
25
1500
1600
1700
1800
1900
2000
Sweden
England and Wales

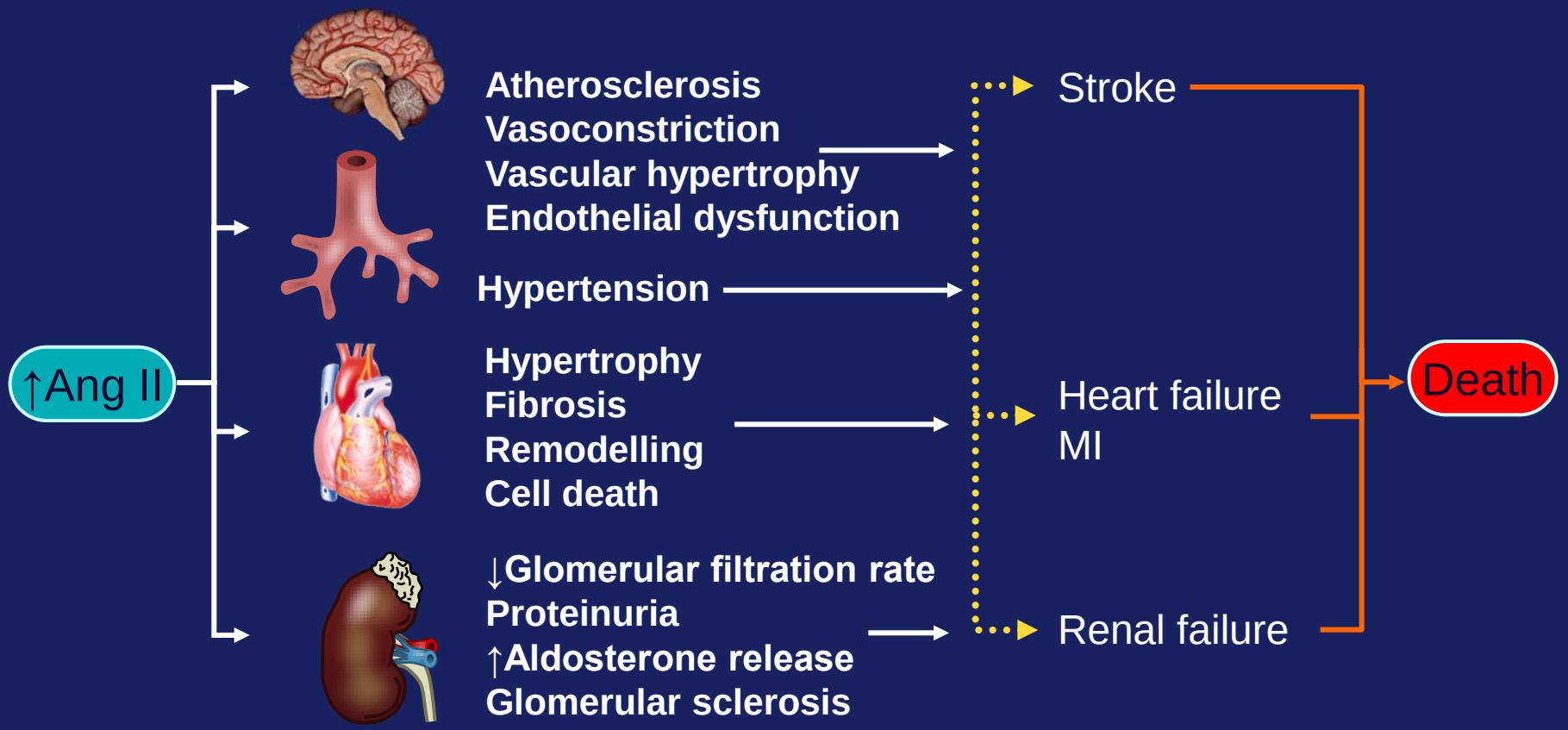

Proteinuria
Apoptosis
Tubular transport
Glomerular hemodynamics
Growth of glomerular and tubular cells
Angiotensin II
Induction of reactive oxygen species
Inhibition of NO synthesis
Induction of chemokines
Metabolic effects
Upregulation of Toll-like 4 receptors
Stimulation of extracellular matrix synthesis, inhibition of extracellular matrix turnover
Increase in tubular HDL and albumin uptake

Increased Ang II has short-term and long-term effects



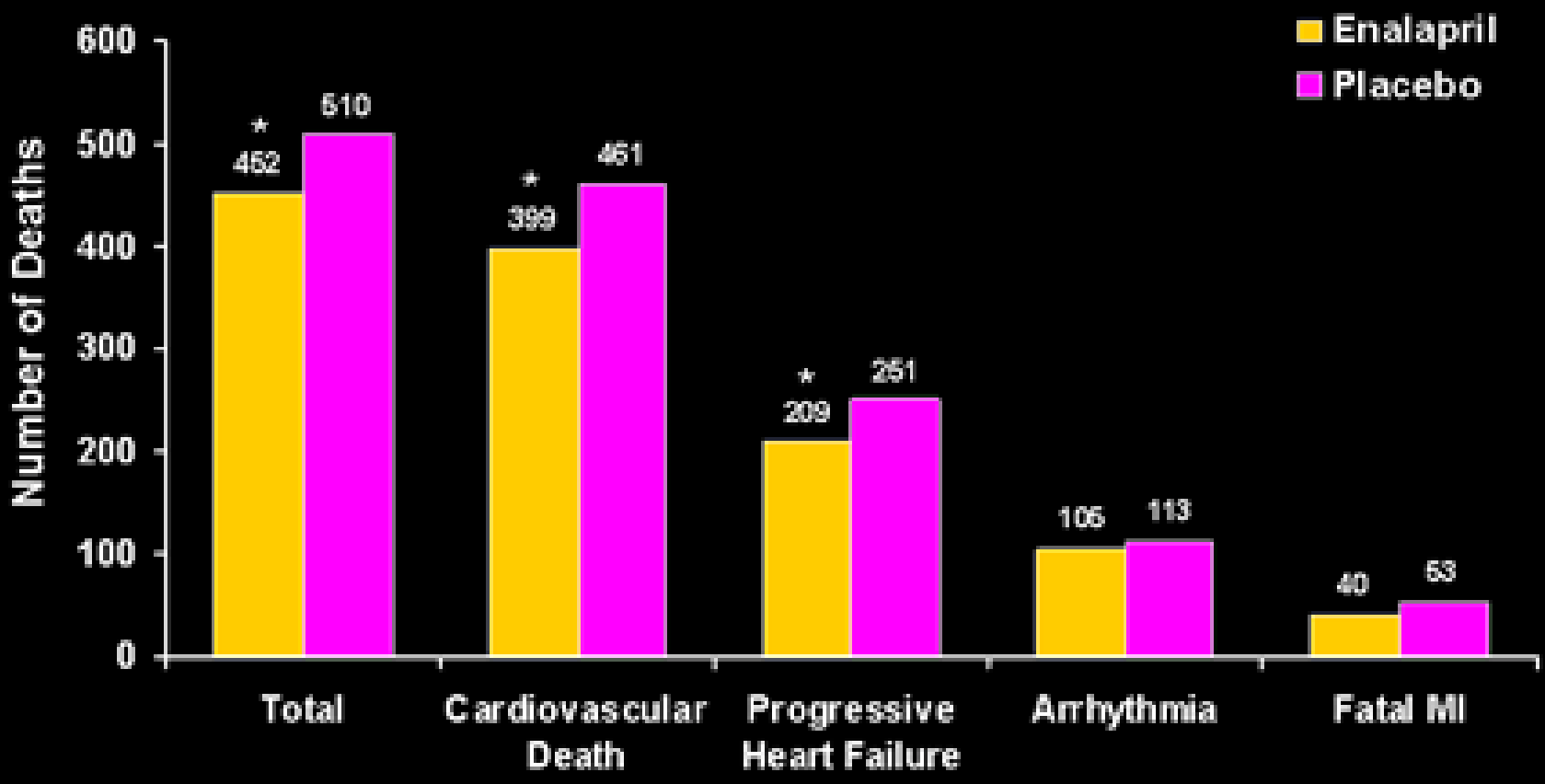
Gibbons GH. 1998; Goodfriend TL. 2003; Arakawa K, *et al*. 2000; Luft FC, *et al*. 1999; Mezzano S, *et al*. 2003.

Chronic activation of the renin system contributes to end-organ damage



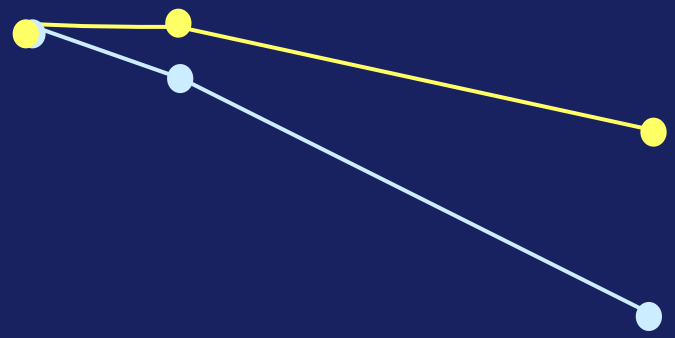
Ang, angiotensin
MI, myocardial infarction

Adapted from Anderson, Goodfriend, and Phillips In: Hypertension Primer, 2003.



The SOLVD Investigators. *N Engl J Med.* 1991;325:293-302.

ACE-I is More Renoprotective than Conventional Therapy in Type 1 Diabetes (Total N = 409)



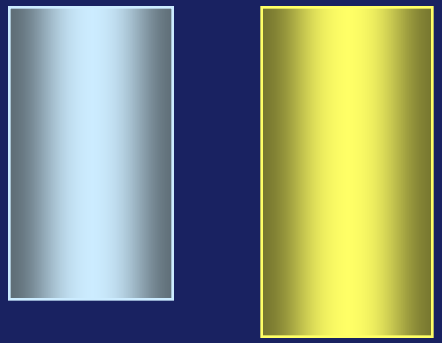
% with Doubling of Baseline Creatinine

Captopril

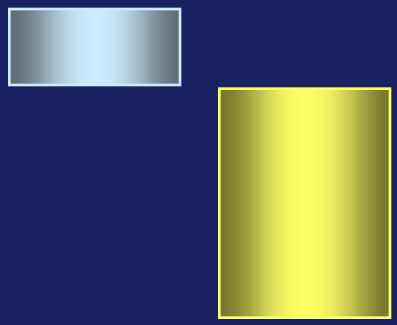
Conventional therapy

Baseline creatinine > 1.5 mg/dl

Decrease in Mean Blood Pressure (mm Hg)

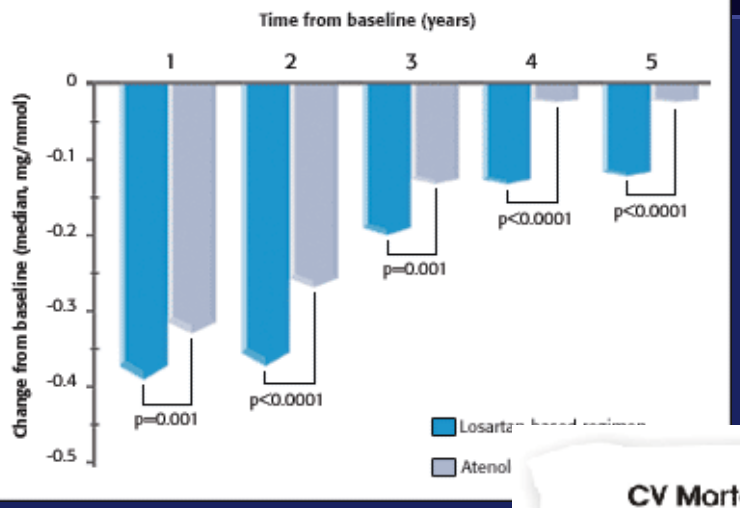


% Reduction in Proteinuria

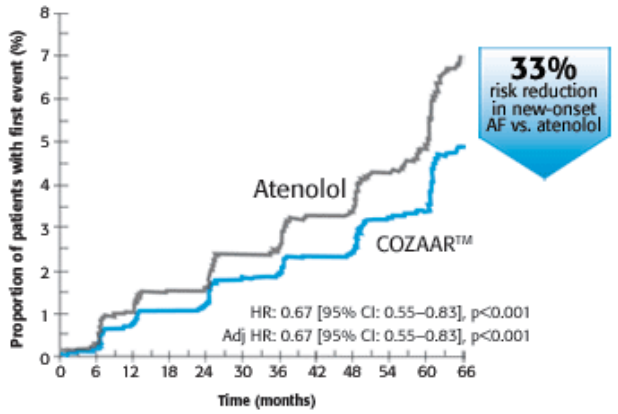


Lewis et al. *N Engl J Med*. 1993;329:1456-1462.

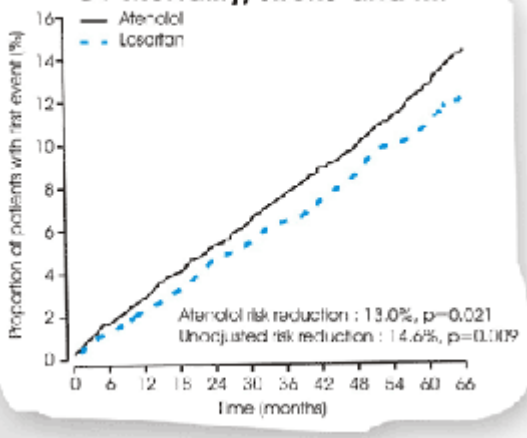
Superior Risk Reduction of Albuminuria[3]
with similar blood pressure reductions



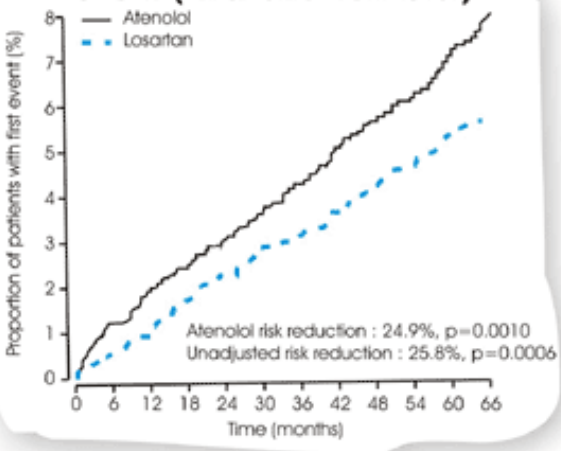
Superior Risk Reduction in New-Onset AF[2]
with similar blood pressure reductions

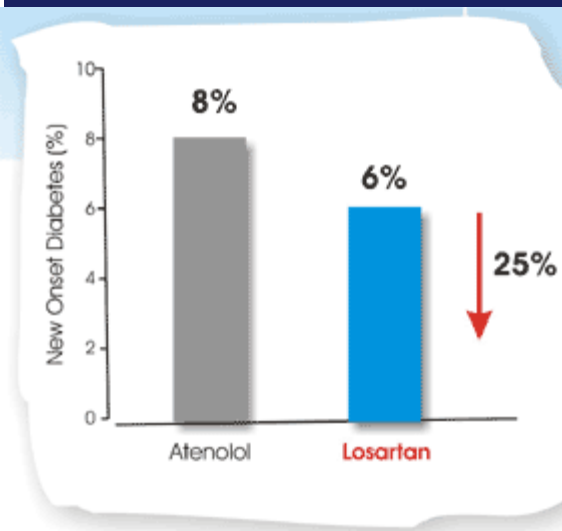


CV Mortality, stroke and MI

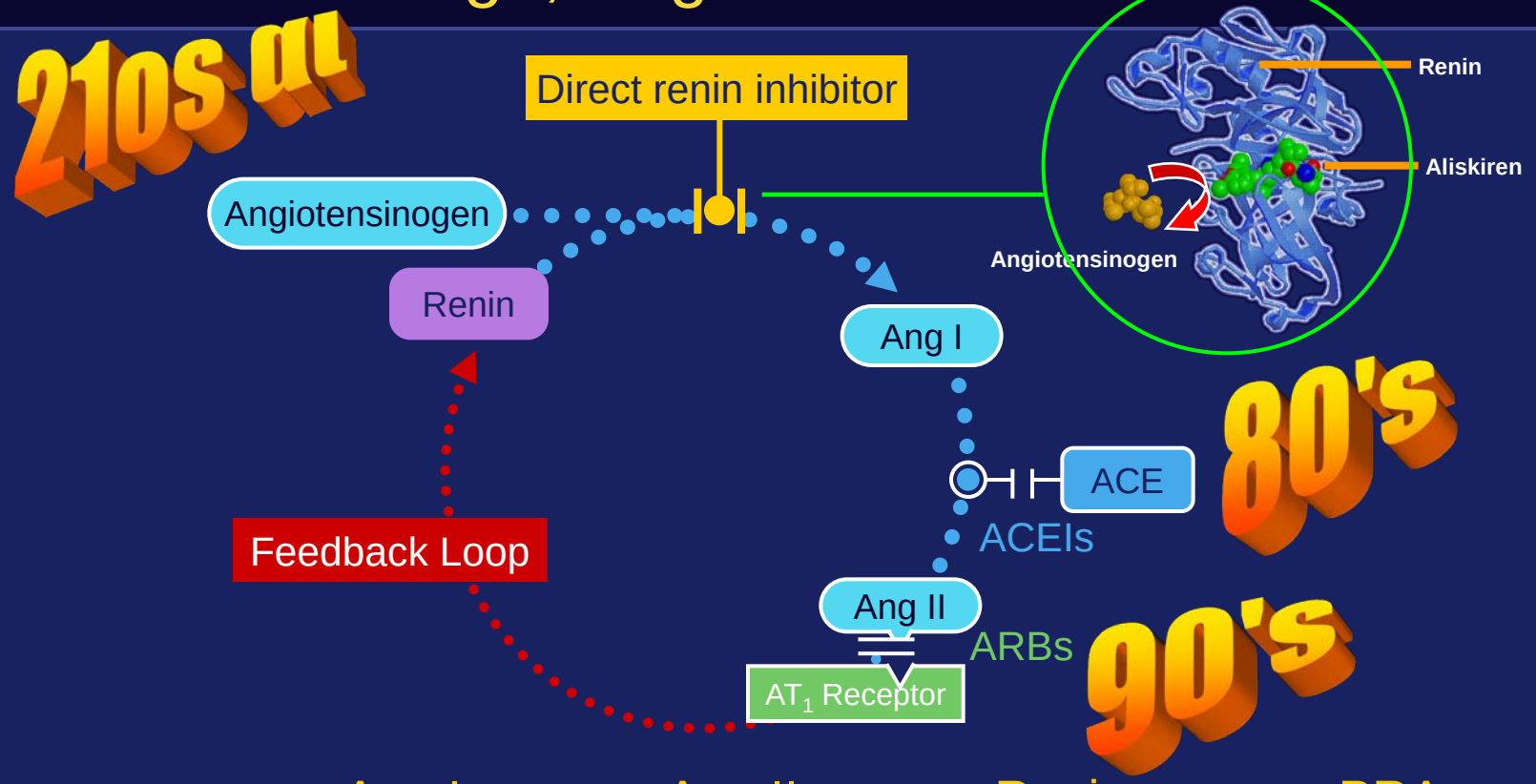


Stroke (fatal and non fatal)





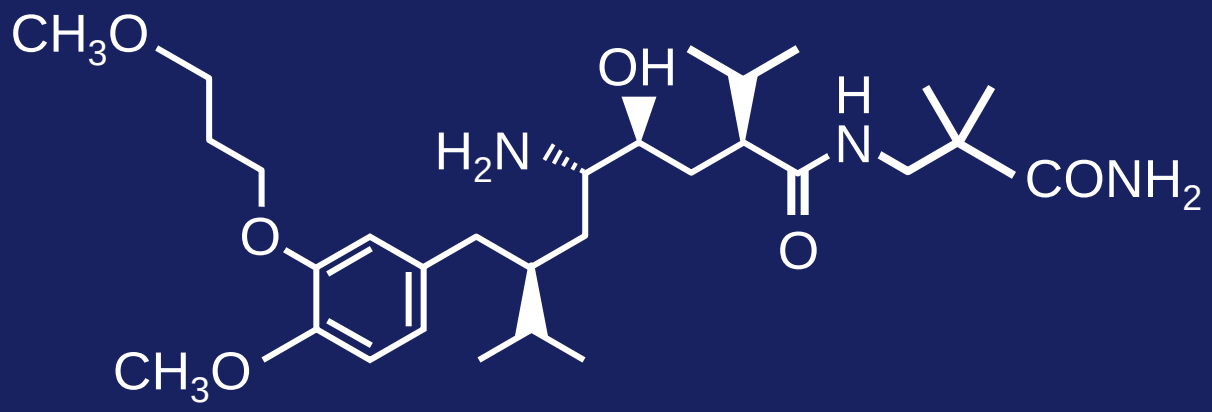
Unlike ACEIs and ARBs, aliskiren reduces Ang I, Ang II and PRA



	Ang I	Ang II	Renin	PRA
ACEI	↑	↓	↑	↑
ARB	↑	↑	↑	↑
Aliskiren	↓	↓	↑	↓

Azizi M *et al*. 2006

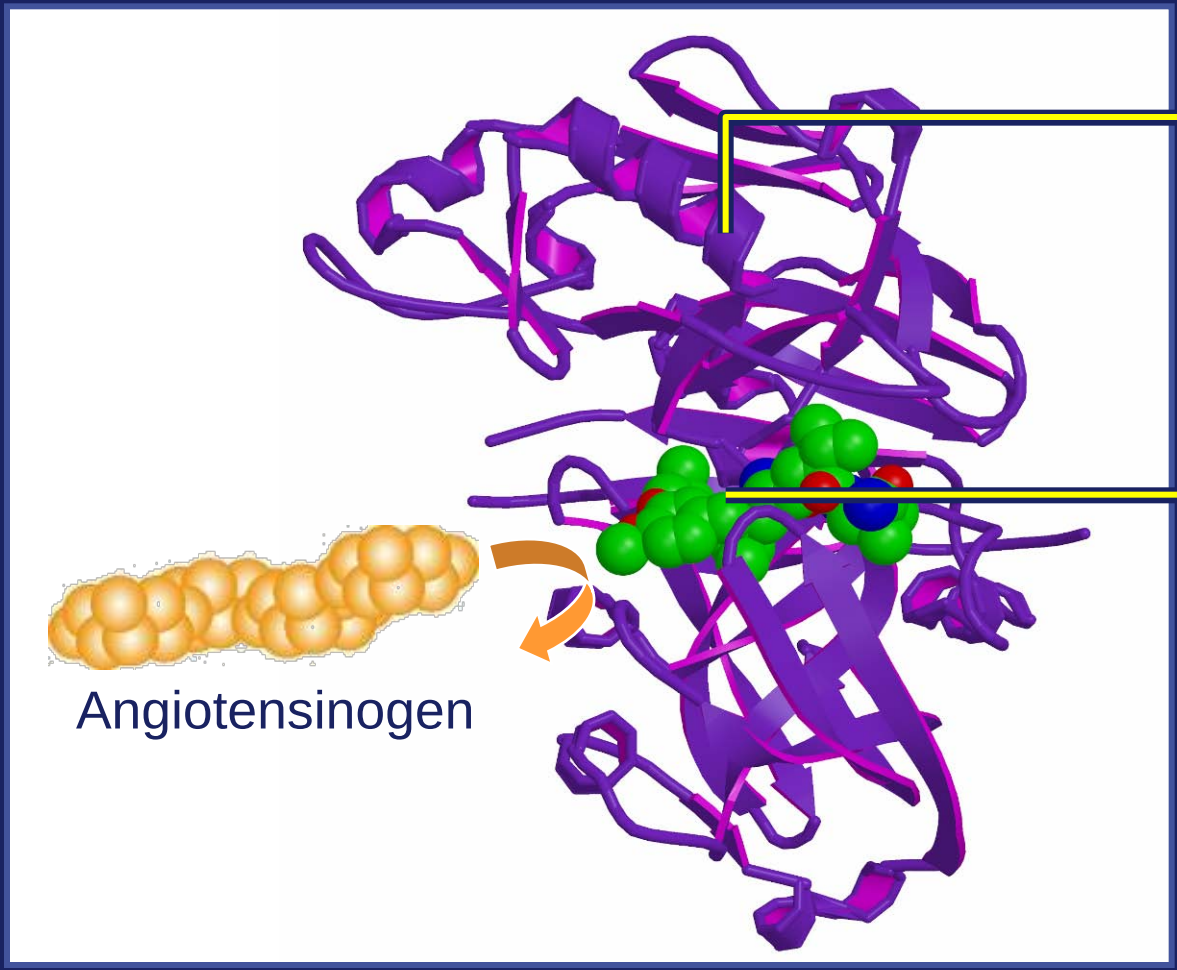
Aliskiren: the first orally available direct renin inhibitor



- Molecular weight = 609.8
- High solubility in water and biological fluids
- Non-peptide drug suitable for oral administration

Wood JM, *et al*. 2003

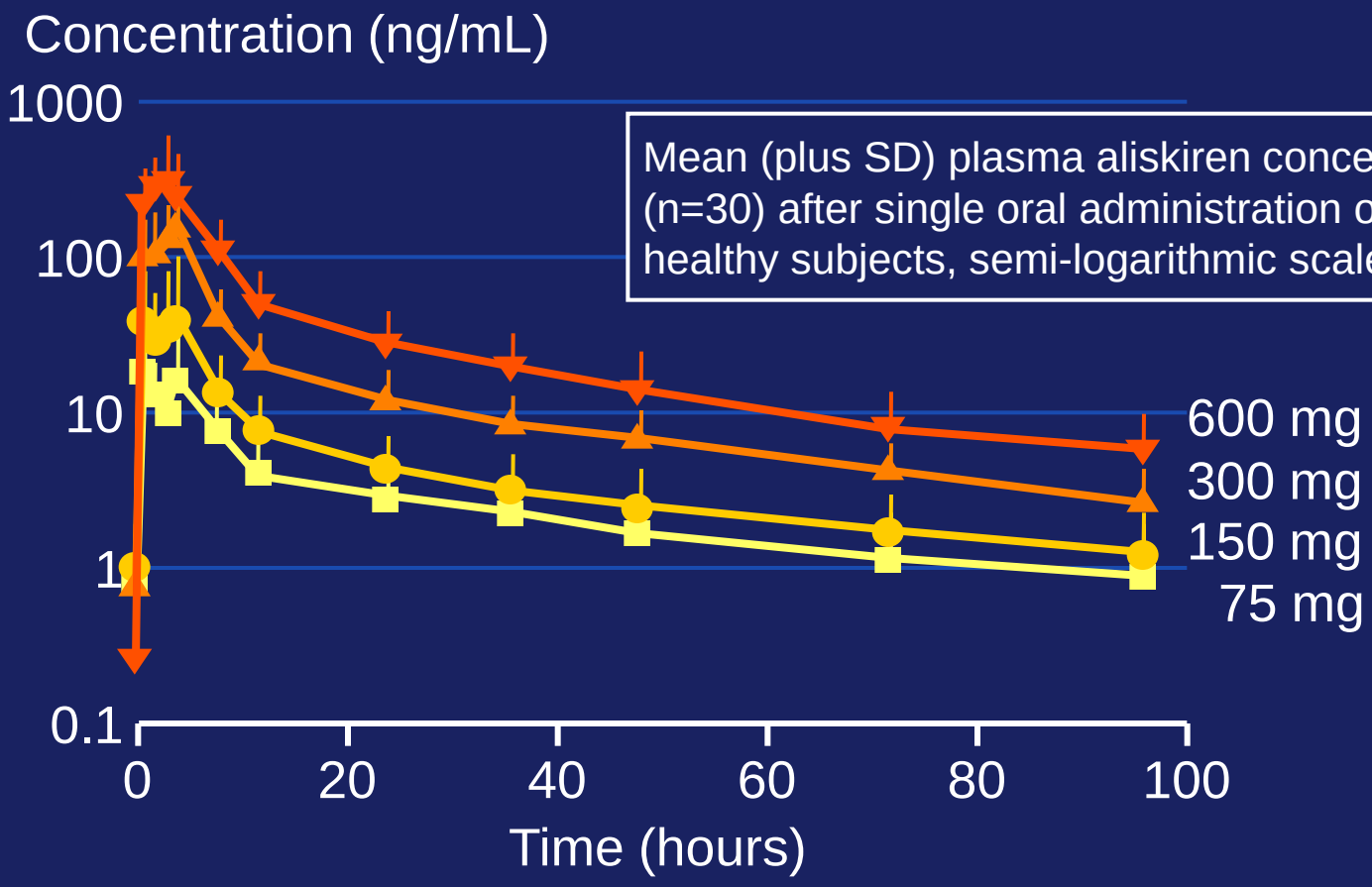
Aliskiren binds to the active site of renin



Aliskiren binds to a pocket in the renin molecule, blocking cleavage of angiotensinogen to angiotensin I

Adapted from Wood JM, *et al.* 2003

Aliskiren has a half-life of approximately 40 hours, making it suitable for once-daily dosing



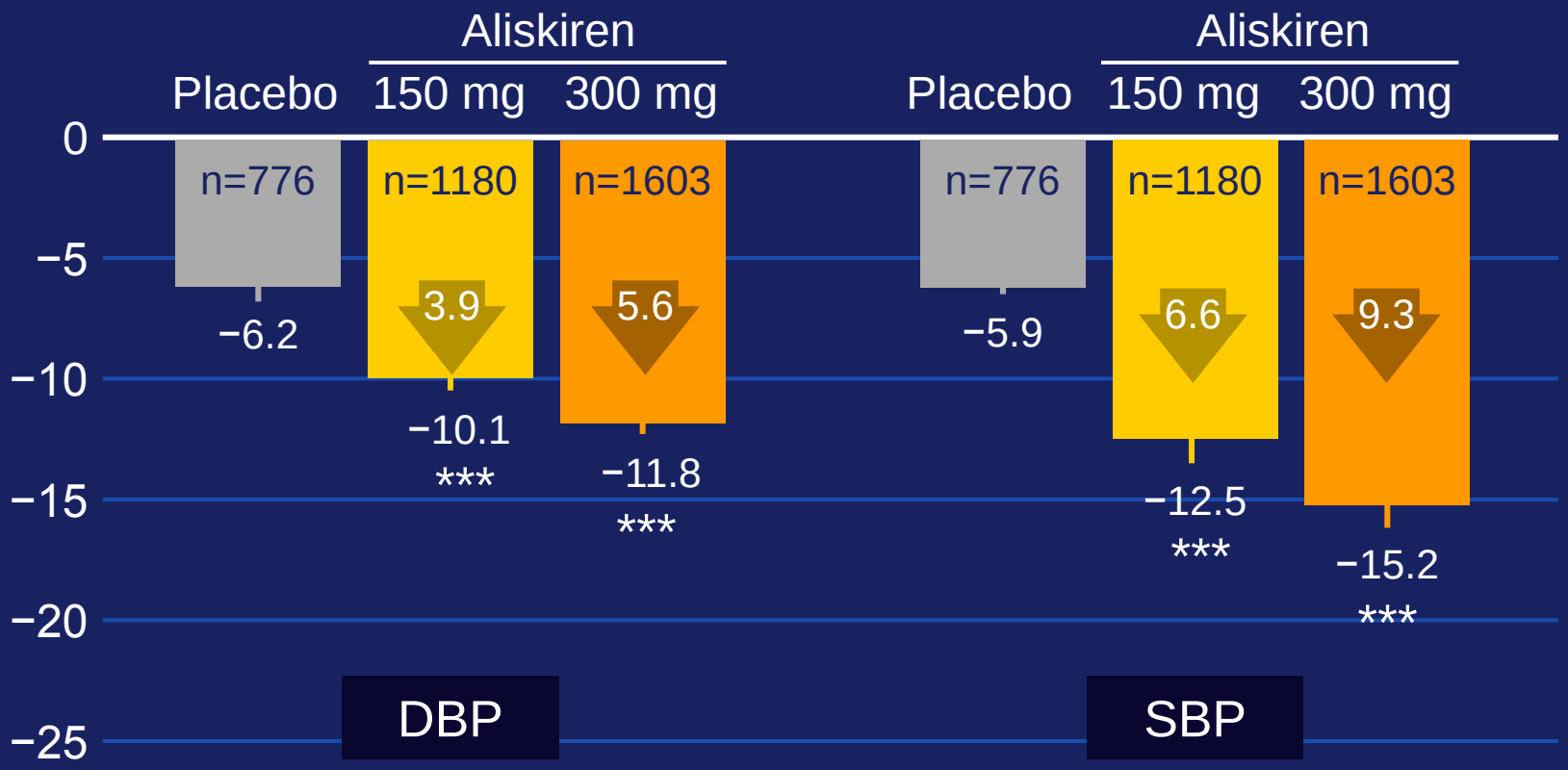
Mean (plus SD) plasma aliskiren concentration profiles (n=30) after single oral administration of aliskiren to healthy subjects, semi-logarithmic scale

Vaidyanathan S, *et al*. 2006 (Study 2205)

Aliskiren profile

- Antihypertensive action
  - Efficacy in monotherapy
  - Efficacy in comparative and add-on studies
  - 24-hour BP control
  - Long-term efficacy
  - Persistence of effect
  - Safety
  - Effects on components of the Renin System
- End-Organ Protection
  - ASPIRE HIGHER program
  - Completed clinical trials
  - Ongoing

Pooled analyses in >3,500 patients demonstrate that aliskiren provides dose-dependent reductions in BP



Mean change from baseline in mean sitting BP (mmHg)

***p<0.0001 vs placebo

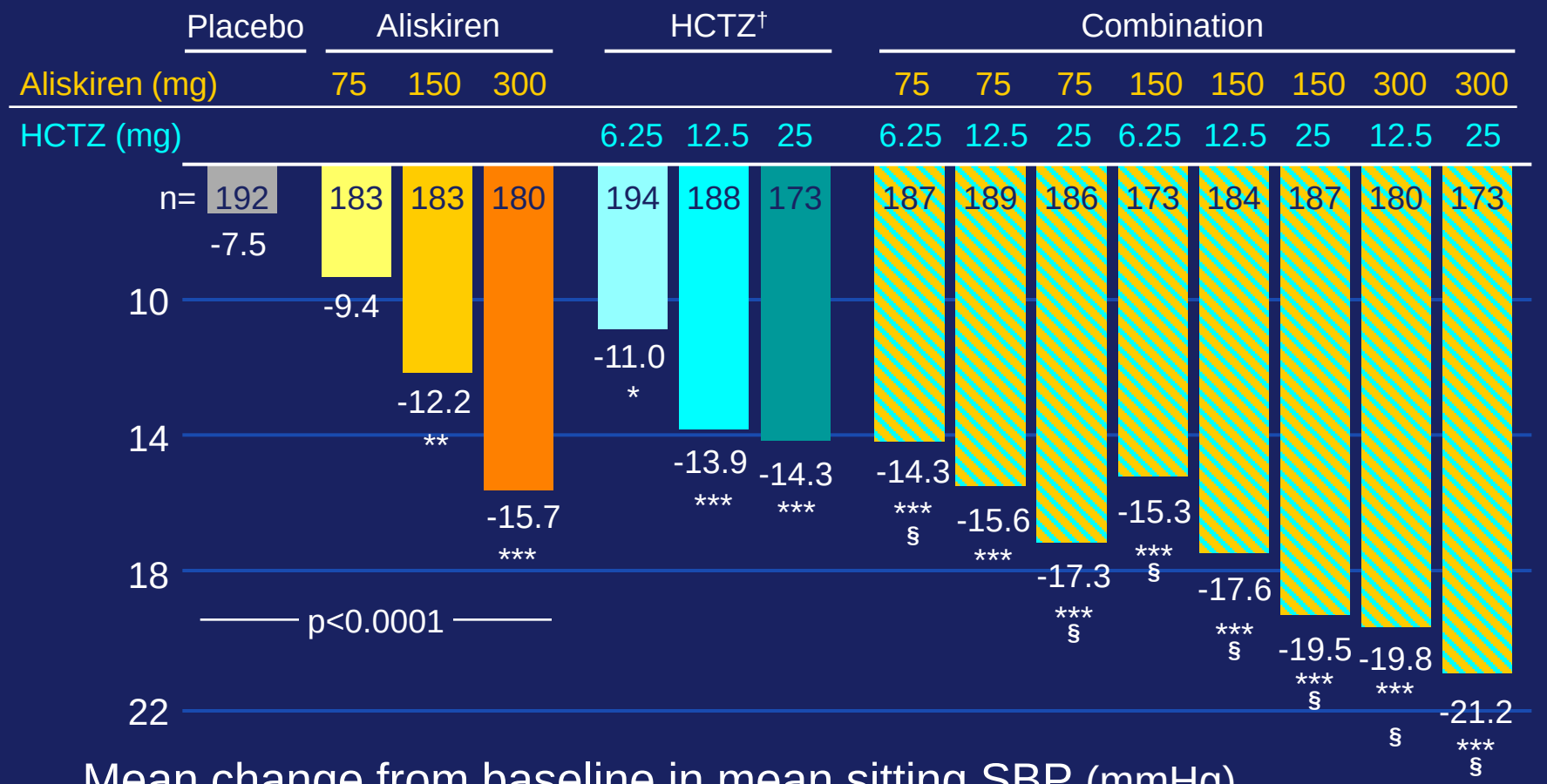
Values under bars represent least square mean reductions ± standard error of the mean; values in arrows represent placebo-subtracted reductions

Dahlöf B, *et al.* 2007 (Pooled analysis)

Aliskiren profile

- The Renin System / The importance of PRA / DRI Mode of Action
- Aliskiren / Clinical PK/PD profile
- Clinical data
  - Efficacy in monotherapy
  - Efficacy in comparative and add-on studies
  - 24-hour BP control
  - Long-term efficacy
  - Persistence of effect
  - Safety
  - Effects on components of the Renin System
- End-Organ Protection
  - ASPIRE HIGHER program
  - Completed clinical trials
  - Ongoing

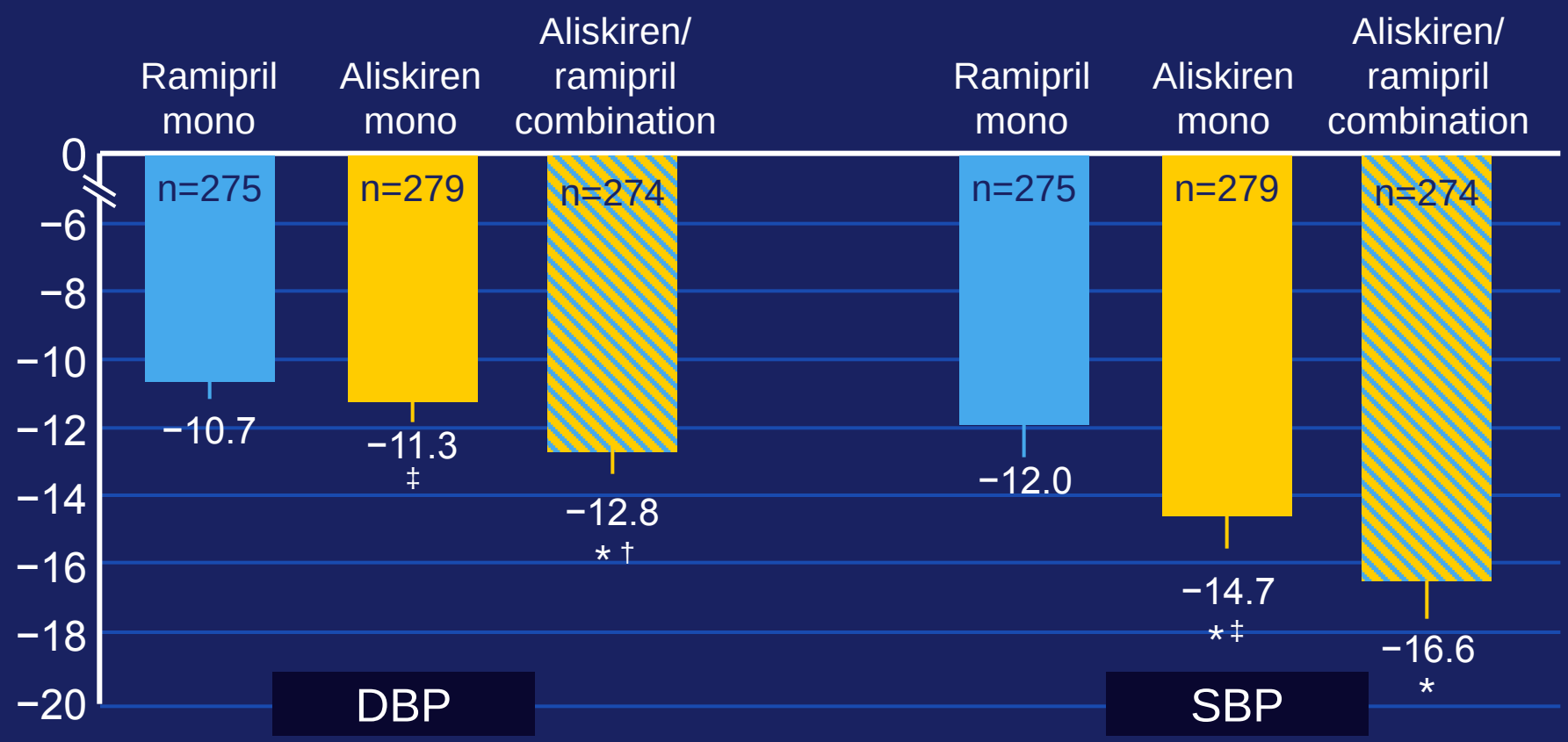
Aliskiren provides additional SBP lowering when combined with HCTZ



†Overall significance of HCTZ effect not tested
Pairwise comparisons:*p<0.05; **p<0.001; ***p<0.0001 vs. placebo;
§ p<0.05 vs. each component monotherapy

Villamil A, *et al*. 2006 (Study 2204)

Aliskiren/ramipril combination provides significantly greater reductions in BP than component monotherapies



Mean change from baseline in mean sitting BP at Week 8 (mmHg)

*p<0.05 for superiority vs ramipril monotherapy; †p<0.05 for superiority vs aliskiren monotherapy;
‡p<0.05 for non-inferiority for aliskiren monotherapy vs ramipril monotherapy
Error bars indicate standard error from the mean

Uresin Y, *et al.* 2007 (Study 2307)

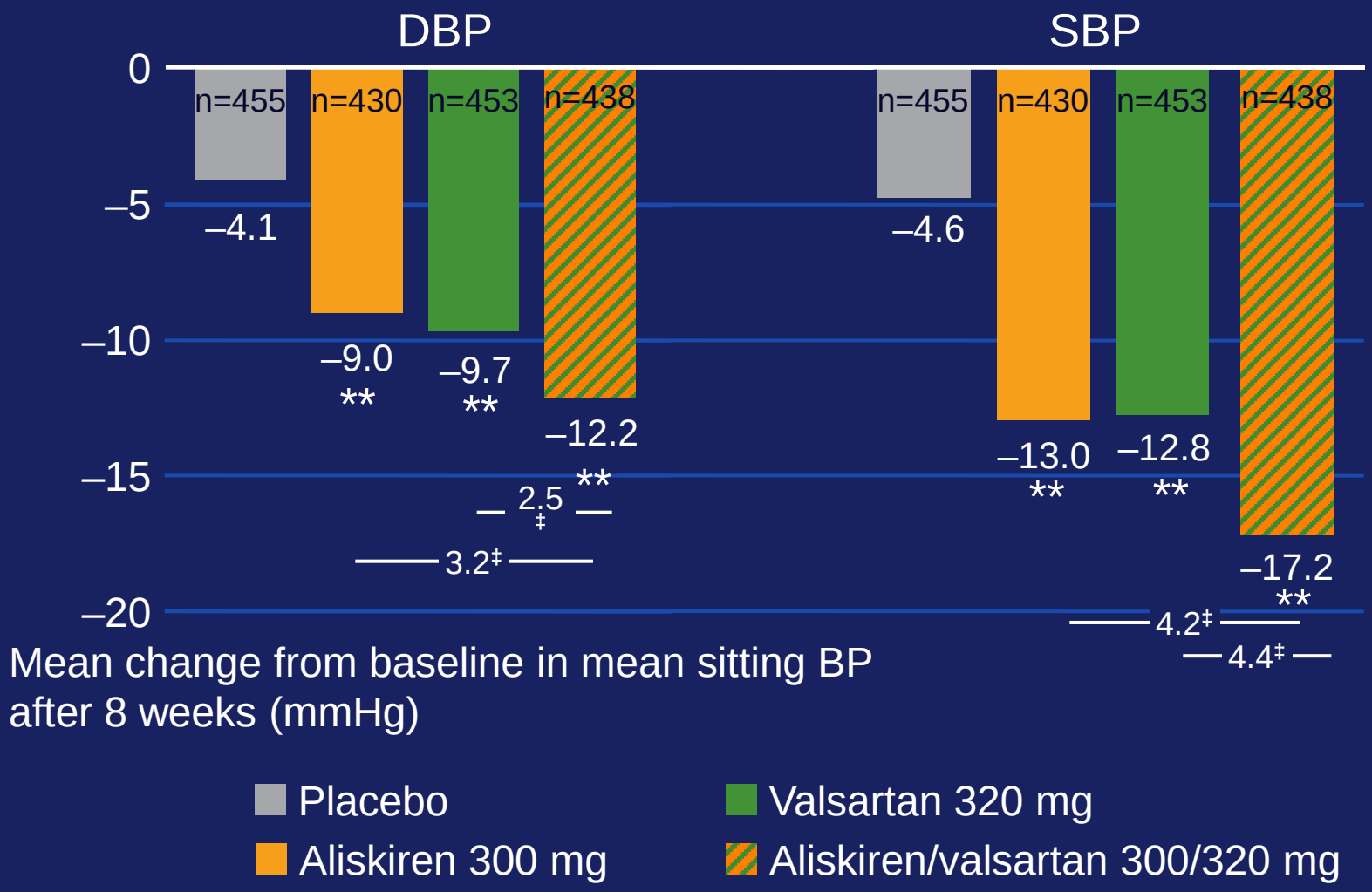
Aliskiren/ramipril combination therapy demonstrates a lower incidence of cough compared with ramipril monotherapy

	Ramipril monotherapy* (n=278)	Aliskiren monotherapy* (n=282)	Aliskiren /ramipril combination therapy* (n=277)
Any AE	33.8	32.3	30.0
Serious AEs	2.2	2.8	1.4
Discontinuation due to AEs	4.0	3.9	2.2
Treatment-related AEs	11.9	7.4	6.1
Most frequent AEs (≥2% in any group)			
Headache	6.1	3.2	2.9
Cough	4.7	2.1	1.8
Nasopharyngitis	1.8	3.2	1.1
Diarrhoea	2.5	1.1	1.1

*Patients received aliskiren 150 mg, ramipril 5 mg, or aliskiren/ramipril 150/5 mg od. After 4 weeks, patients were titrated to aliskiren 300 mg, ramipril 10 mg or aliskiren/ramipril 300/5 mg for an additional 4 weeks

Uresin Y, *et al.* 2006 (Study 2307)

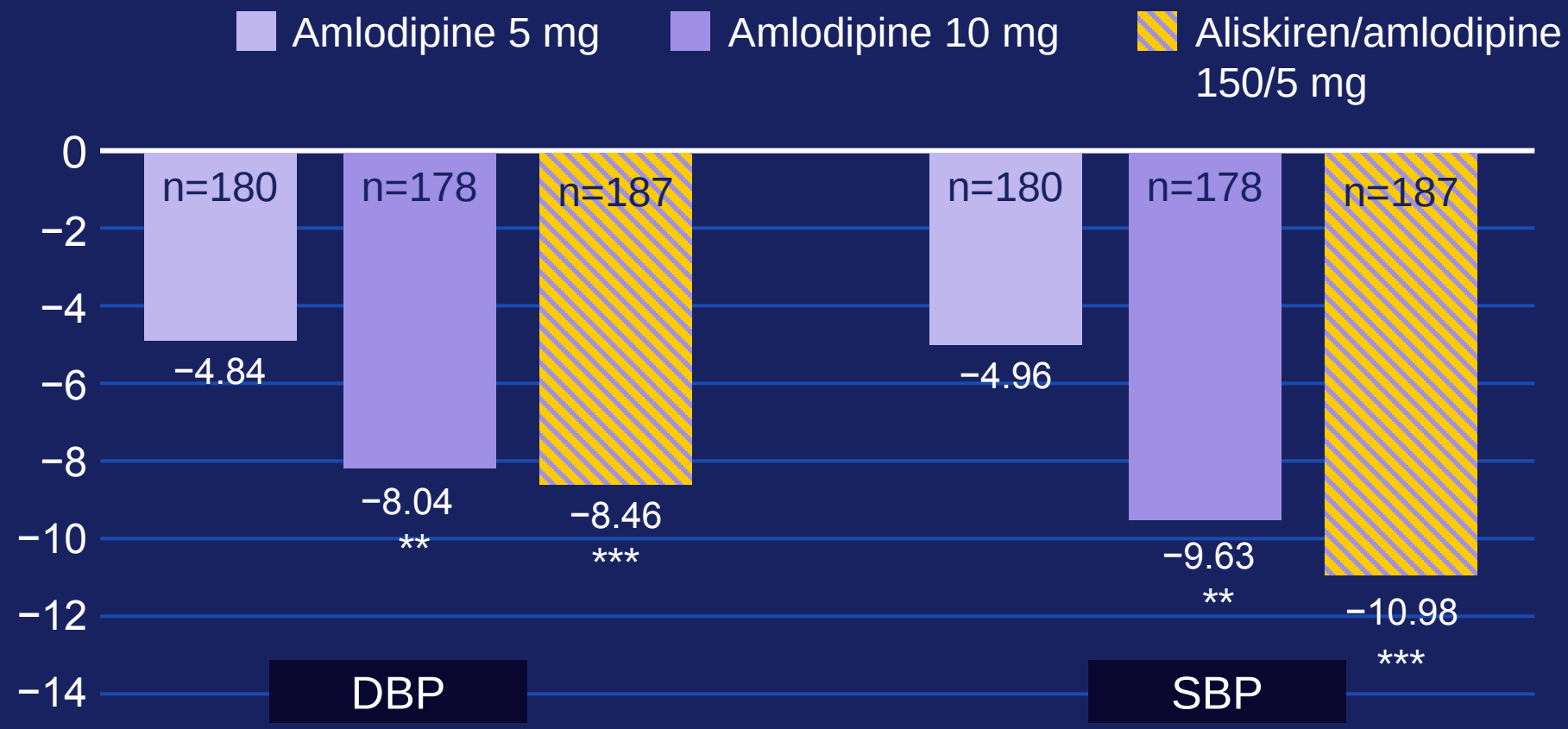
Aliskiren/valsartan combination therapy provides significantly greater BP reductions than either component monotherapy



**p<0.0001 vs placebo; ‡p<0.0001 vs aliskiren/valsartan combination therapy

Oparil S, *et al*. 2007 (Study 2327)

Aliskiren significantly improves BP control when added to amlodipine 5 mg

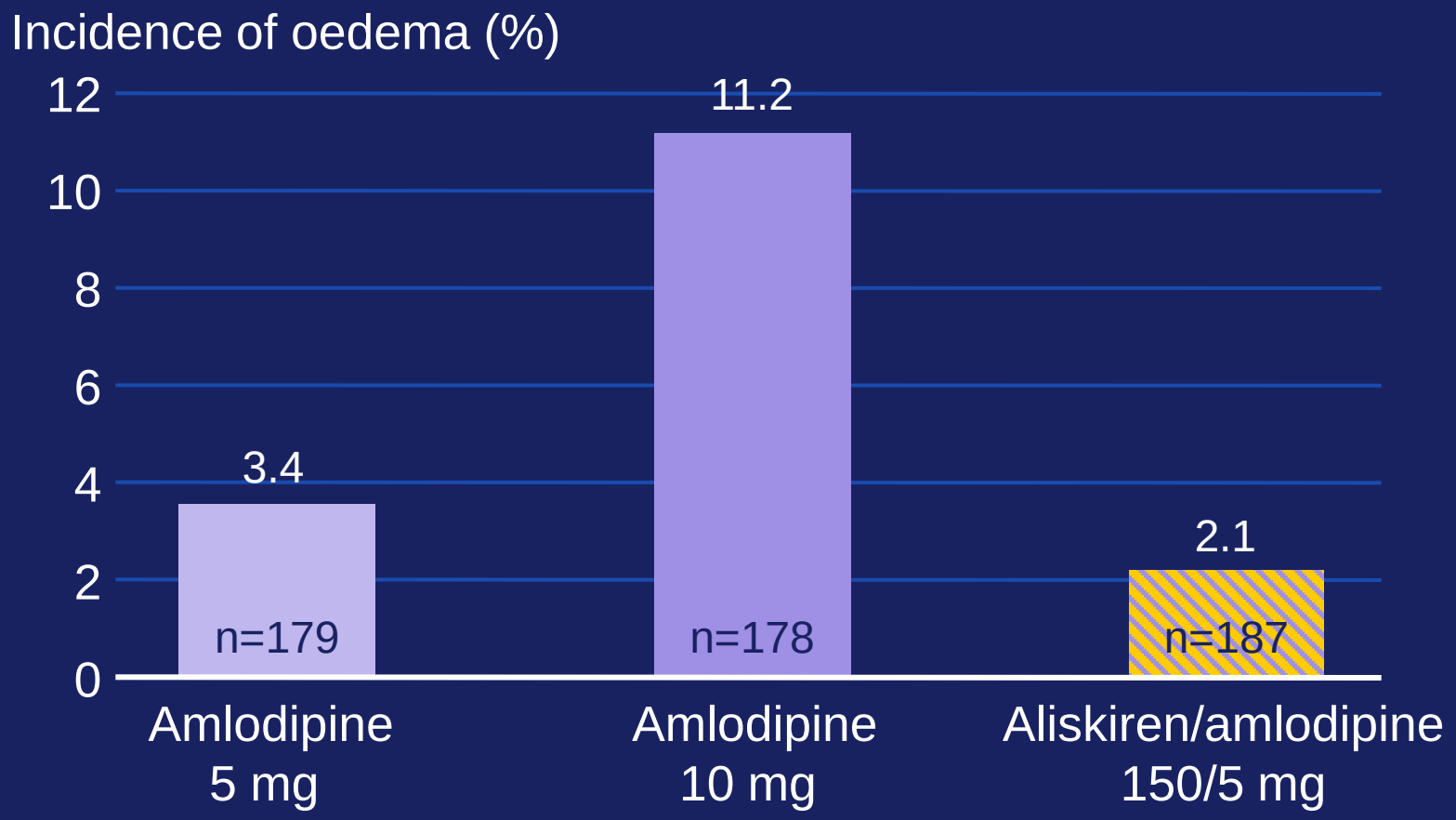


Mean change from baseline in mean sitting BP (mmHg)

**p=0.002, ***p<0.0001 vs amlodipine 5 mg

Drummond W, *et al.* 2007 (Study 2305)

Addition of aliskiren to amlodipine causes fewer incidences of oedema than increasing the amlodipine dosage

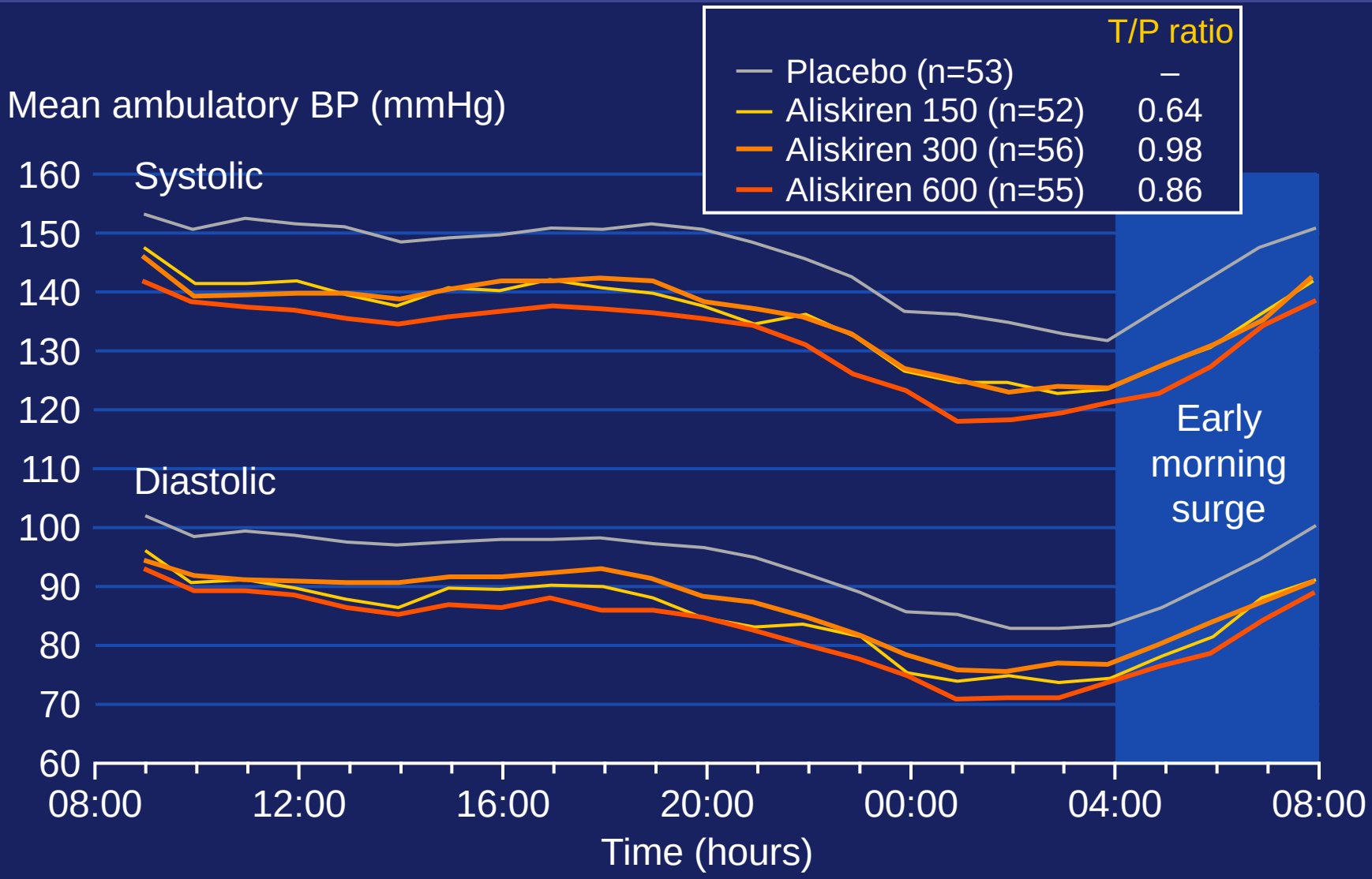


Drummond W, *et al.* 2007 (Study 2305)

Aliskiren profile

- The Renin System / The importance of PRA / DRI Mode of Action
- Aliskiren / Clinical PK/PD profile
- Clinical data
  - Efficacy in monotherapy
  - Efficacy in comparative and add-on studies
  - 24-hour BP control
  - Long-term efficacy
  - Persistence of effect
  - Safety
  - Effects on components of the Renin System
- End-Organ Protection
  - ASPIRE HIGHER program
  - Completed clinical trials
  - Ongoing

Aliskiren provides sustained 24-hour BP control



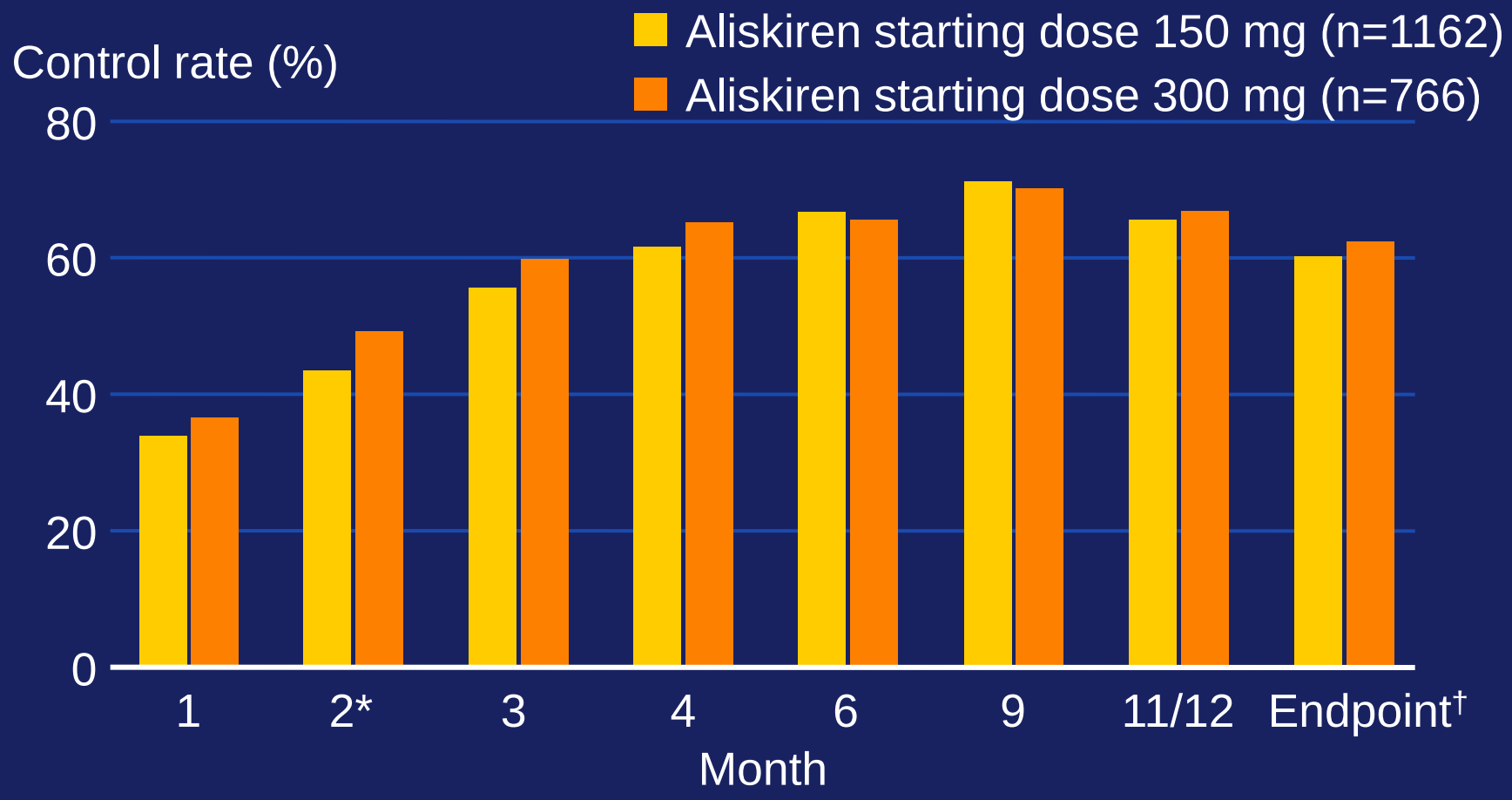
T/P: trough/peak

Ruilope LM, *et al.* 2007 (Pooled analysis)

Aliskiren profile

- The Renin System / The importance of PRA / DRI Mode of Action
- Aliskiren / Clinical PK/PD profile
- Clinical data
  - Efficacy in monotherapy
  - Efficacy in comparative and add-on studies
  - 24-hour BP control
  - Long-term efficacy
  - Persistence of effect
  - Safety
  - Effects on components of the Renin System
- End-Organ Protection
  - ASPIRE HIGHER program
  - Completed clinical trials
  - Ongoing

Aliskiren provides high BP control rates when used long-term



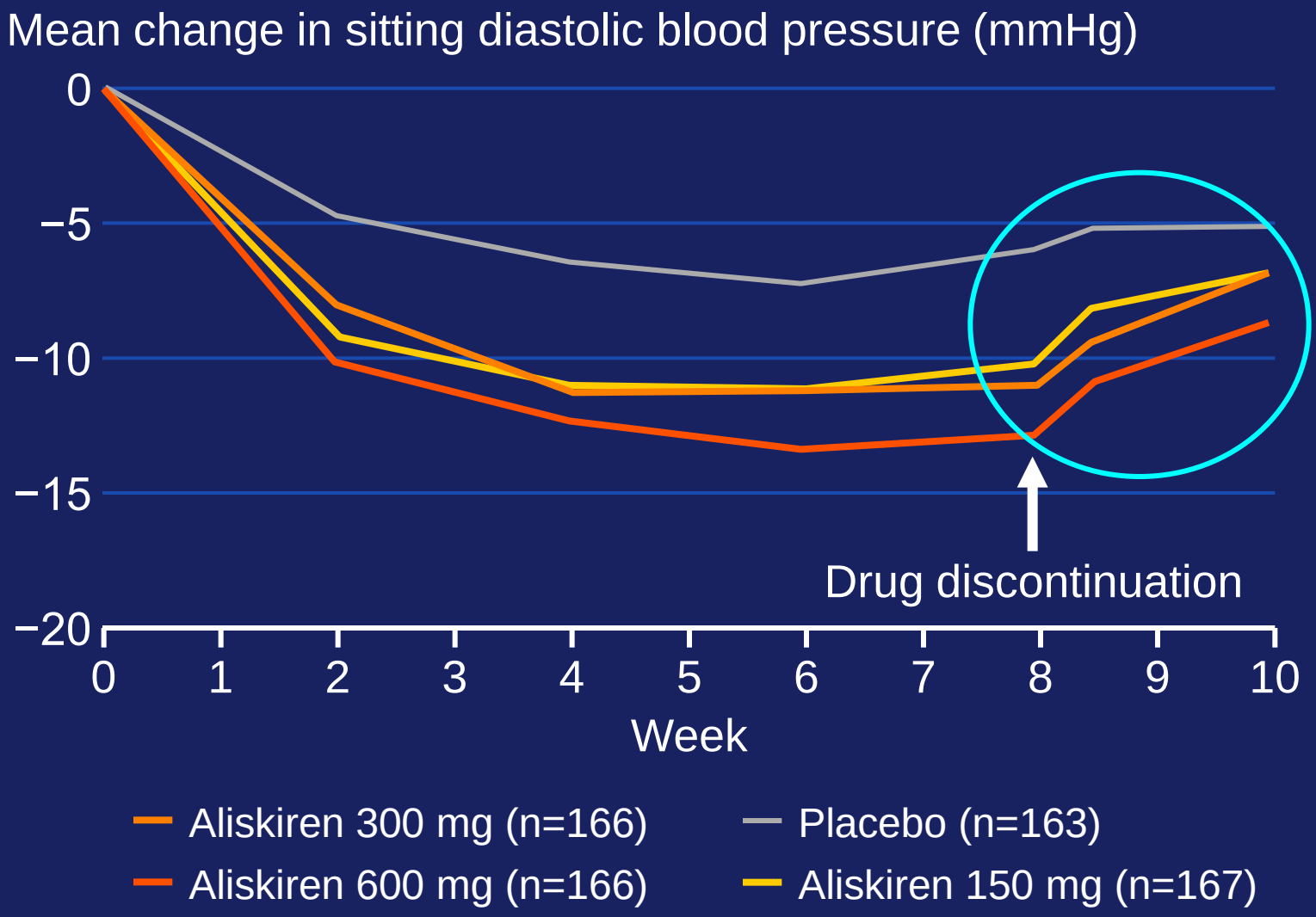
*After month 2, dose titration or addition of HCTZ could occur
†Endpoint is Month 11/12 or last visit carried forward
Control = BP <140/90 mmHg

Sica D, *et al.* 2006 (Study 2302)

Aliskiren profile

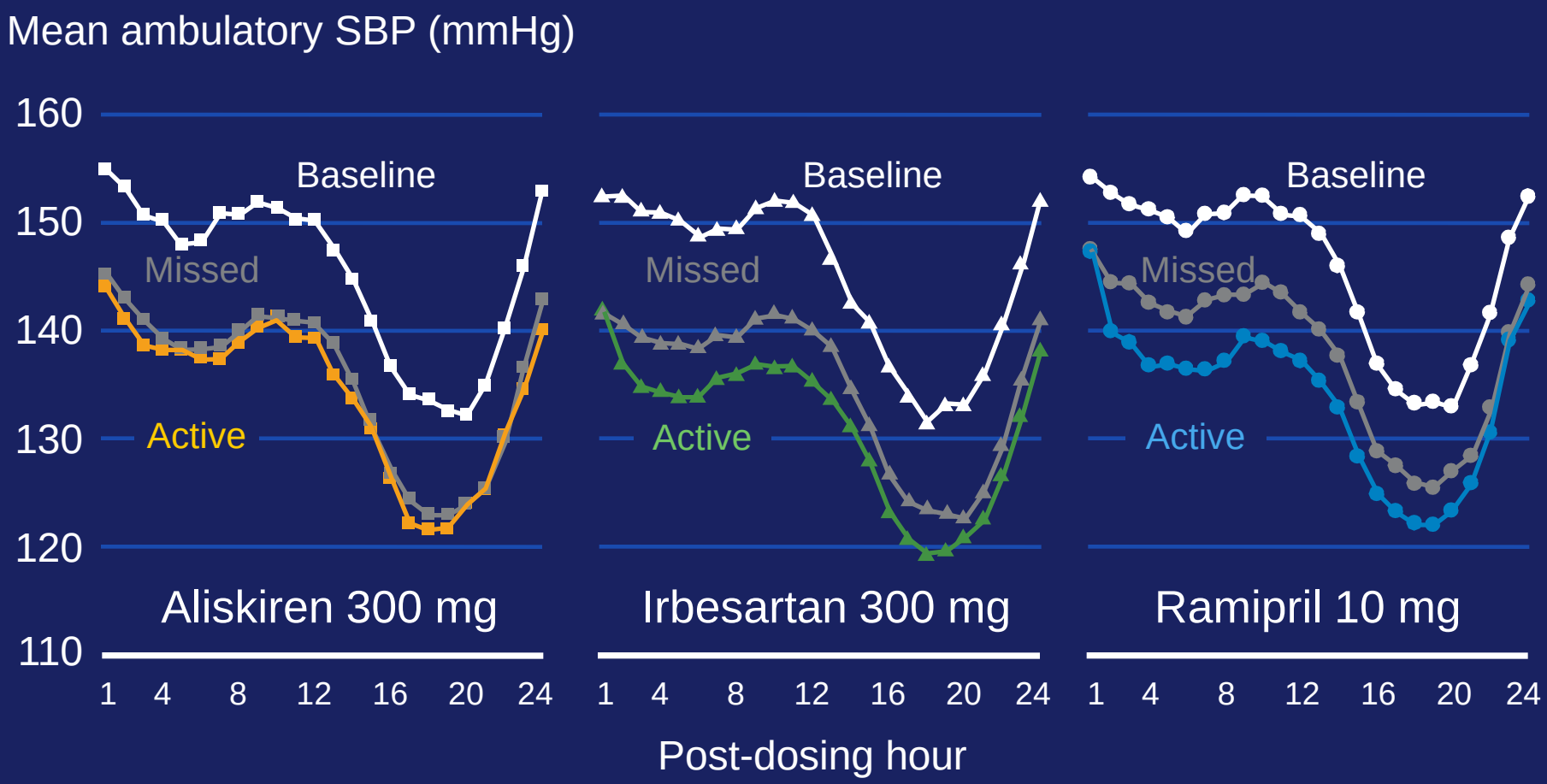
- The Renin System / The importance of PRA / DRI Mode of Action
- Aliskiren / Clinical PK/PD profile
- Clinical data
  - Efficacy in monotherapy
  - Efficacy in comparative and add-on studies
  - 24-hour BP control
  - Long-term efficacy
  - Persistence of effect
  - Safety
  - Effects on components of the Renin System
- End-Organ Protection
  - ASPIRE HIGHER program
  - Completed clinical trials
  - Ongoing

Aliskiren provides prolonged BP-lowering



Herron J, *et al*. 2006 (Study 2308)

Change in ambulatory SBP from active dose to missed dose is numerically smaller with aliskiren than irbesartan or ramipril



Data are shown as hourly mean values for the ABPM completer population

Palatini P, *et al*. 2008 (Study 2351)

Aliskiren profile

- The Renin System / The importance of PRA / DRI Mode of Action
- Aliskiren / Clinical PK/PD profile
- Clinical data
  - Efficacy in monotherapy
  - Efficacy in comparative and add-on studies
  - 24-hour BP control
  - Long-term efficacy
  - Persistence of effect
  - Safety
  - Effects on components of the Renin System
- End-Organ Protection
  - ASPIRE HIGHER program
  - Completed clinical trials
  - Ongoing

Aliskiren monotherapy exhibits tolerability comparable to placebo up to 300 mg once daily

	Placebo n = 781	Aliskiren 75 mg n = 478	Aliskiren 150 mg n = 774	Aliskiren 300 mg n = 768	Aliskiren 600 mg n = 296	All aliskiren n = 2316
Any SAE, n (%)	5 (0.6)	3 (0.6)	3 (0.4)	4 (0.5)	1 (0.3)	11 (0.5)
Any AE, n (%)	314 (40.2)	193 (40.4)	290 (37.5)	309 (40.2)	130 (43.9)	922 (39.8)
Discontinuations due to AE, n (%)	27 (3.5)	8 (1.7)	12 (1.6)	20 (2.6)	5 (1.7)	45 (1.9)
Adverse events, reported by ≥2% of patients for aliskiren monotherapy overall, n (%)						
Headache	68 (8.7)	31 (6.5)	42 (5.4)*	44 (5.7)*	15 (5.1)	132 (5.7)**
Nasopharyngitis	45 (5.8)	34 (7.1)	33 (4.3)	29 (3.8)	5 (1.7)**	101 (4.4)
Diarrhoea	9 (1.2)	6 (1.3)	9 (1.2)	18 (2.3)	28 (9.5)†	61 (2.6)*

AE, adverse event; SAE, serious adverse event. *p<0.05; **p<0.01; †p<0.0001 vs placebo

Weir M, *et al.* 2007 (Pooled analysis)


ΕΥΧΑΡΙΣΤΩ