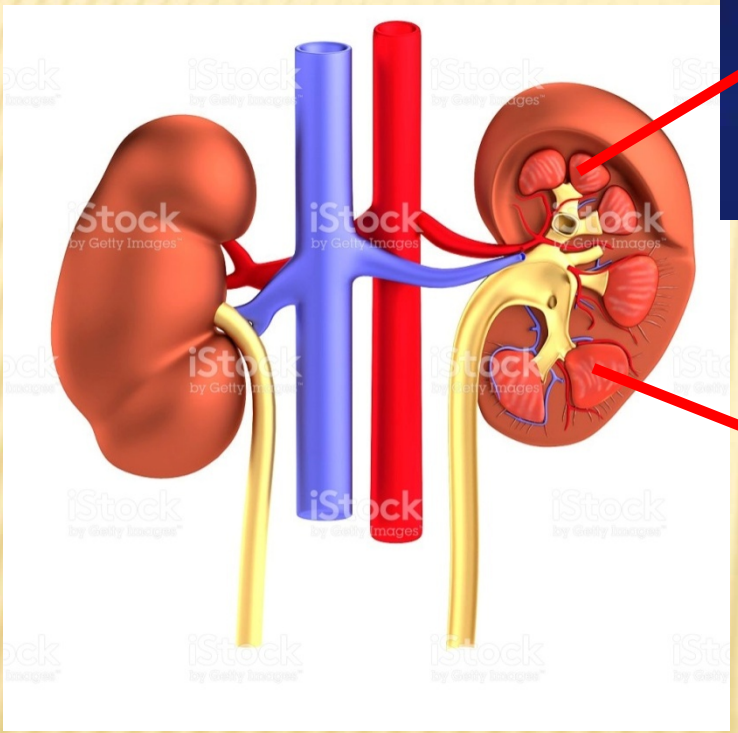
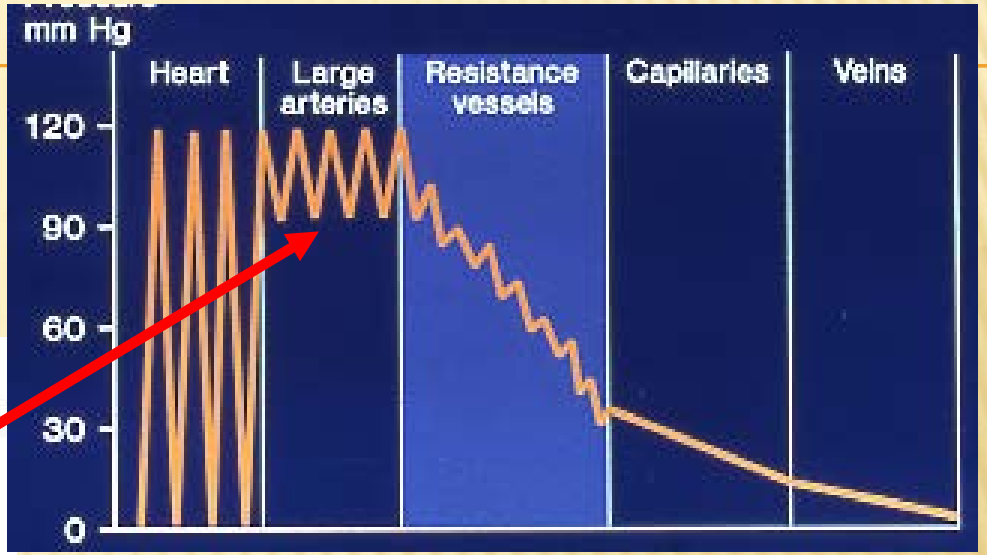
ΤΟ ΣΥΣΤΗΜΑ ΡΕΝΙΝΗΣ-ΑΓΓΕΙΟΤΑΣΙΝΗΣ ΩΣ ΡΥΘΜΙΣΤΗΣ ΤΗΣ ΕΡΥΘΡΟΠΟΙΗΣΗΣ: ΕΠΙΠΤΩΣΕΙΣ ΑΠΌ ΤΗΝ ΑΝΑΣΤΟΛΗ ΤΟΥ

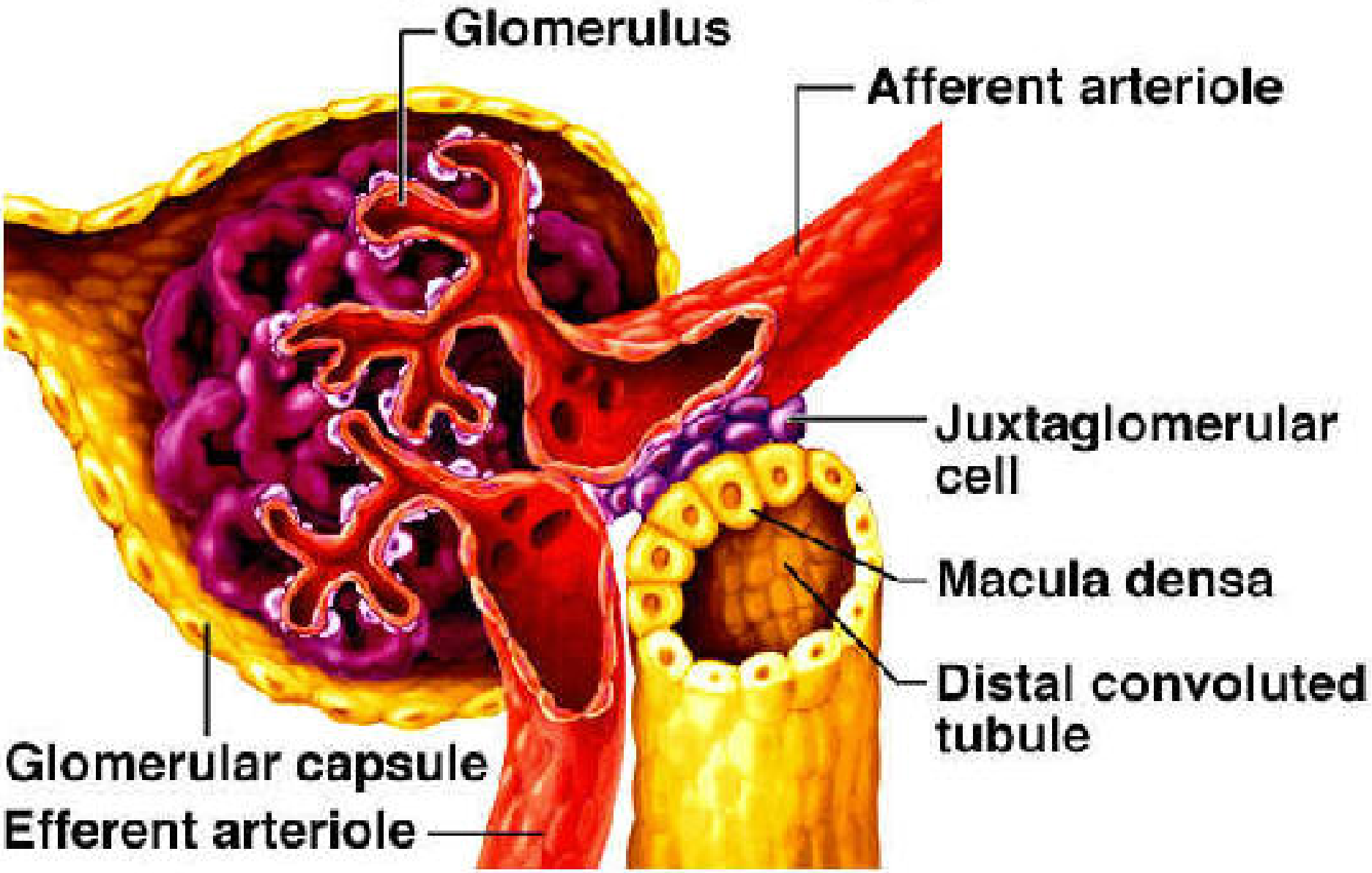
Δημήτριος Β. Βλαχάκος
Καθηγητής Παθολογίας – Νεφρολογίας ΕΚΠΑ
Ιατρική Σχολή Αθηνών
Υπεύθυνος Νεφρολογικής Μονάδας
Β' Προπαιδευτική Παθολογική Κλινική
Πανεπιστημιακό Γ. Ν. «ΑΤΤΙΚΟΝ»



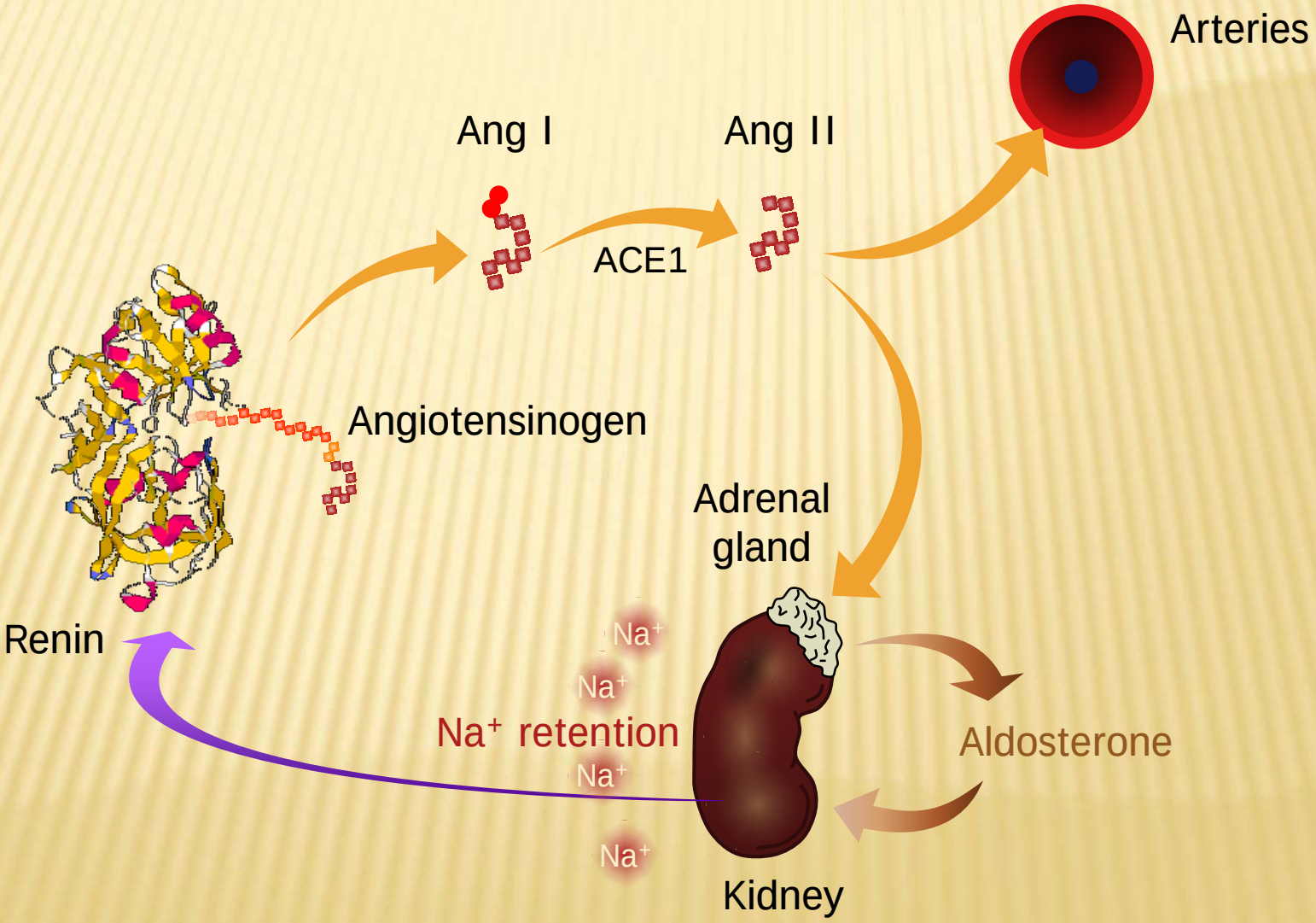

mm Hg
Heart
Large arteries
Resistance vessels
Capillaries
Veins
120
90
60
30
0


Plasma 55%
Formed elements 45%

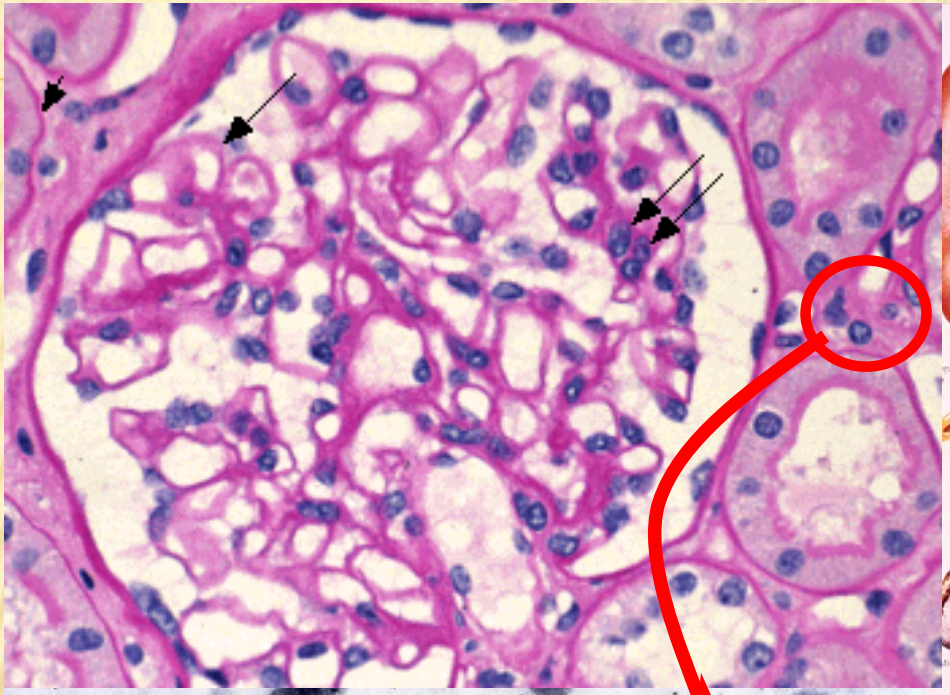
Juxtaglomerular Apparatus

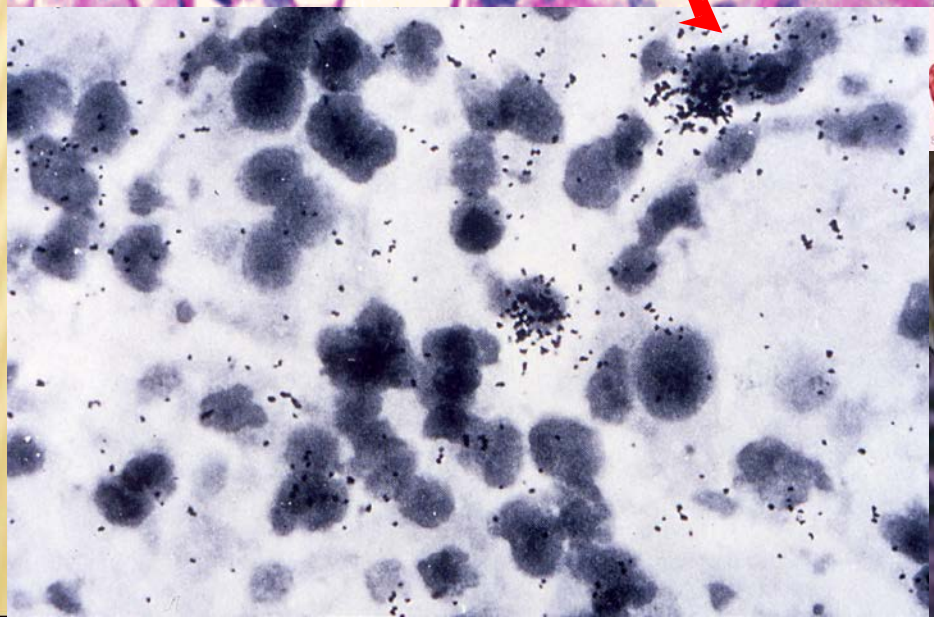


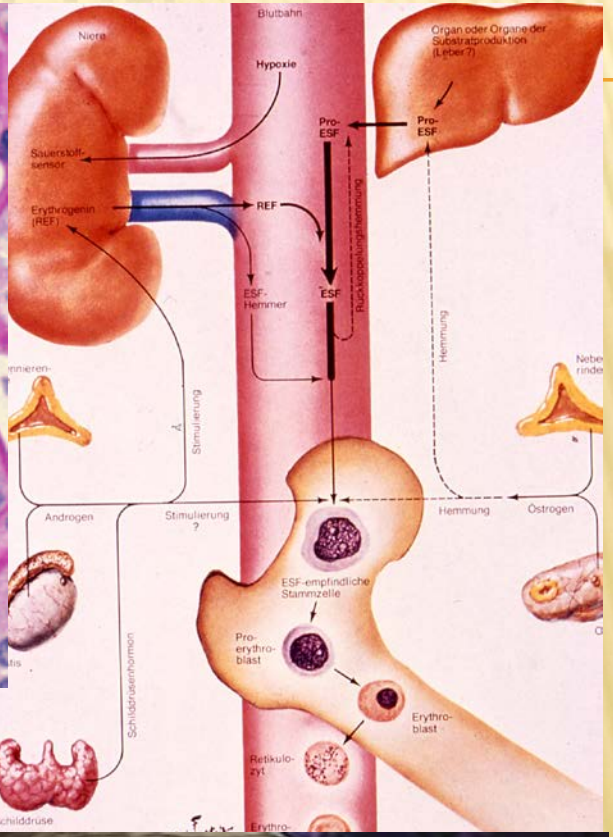
Renin Angiotensin Aldosterone System

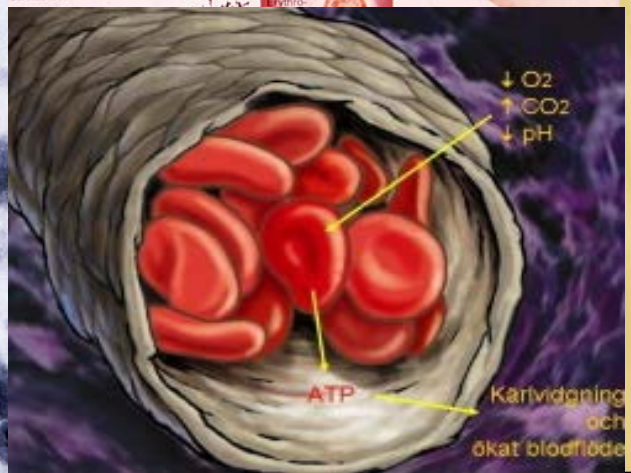


ERYTHROPOETIN





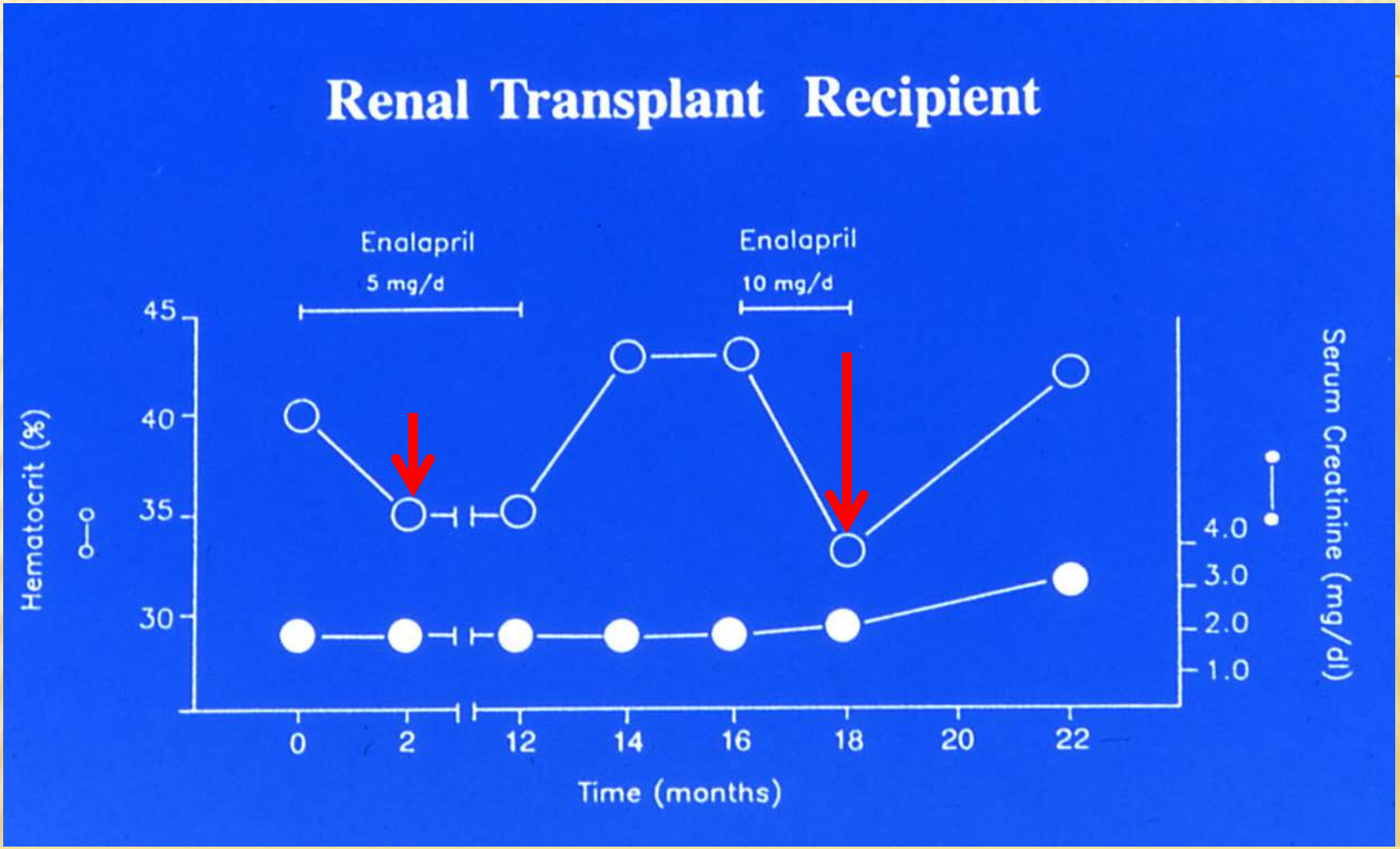




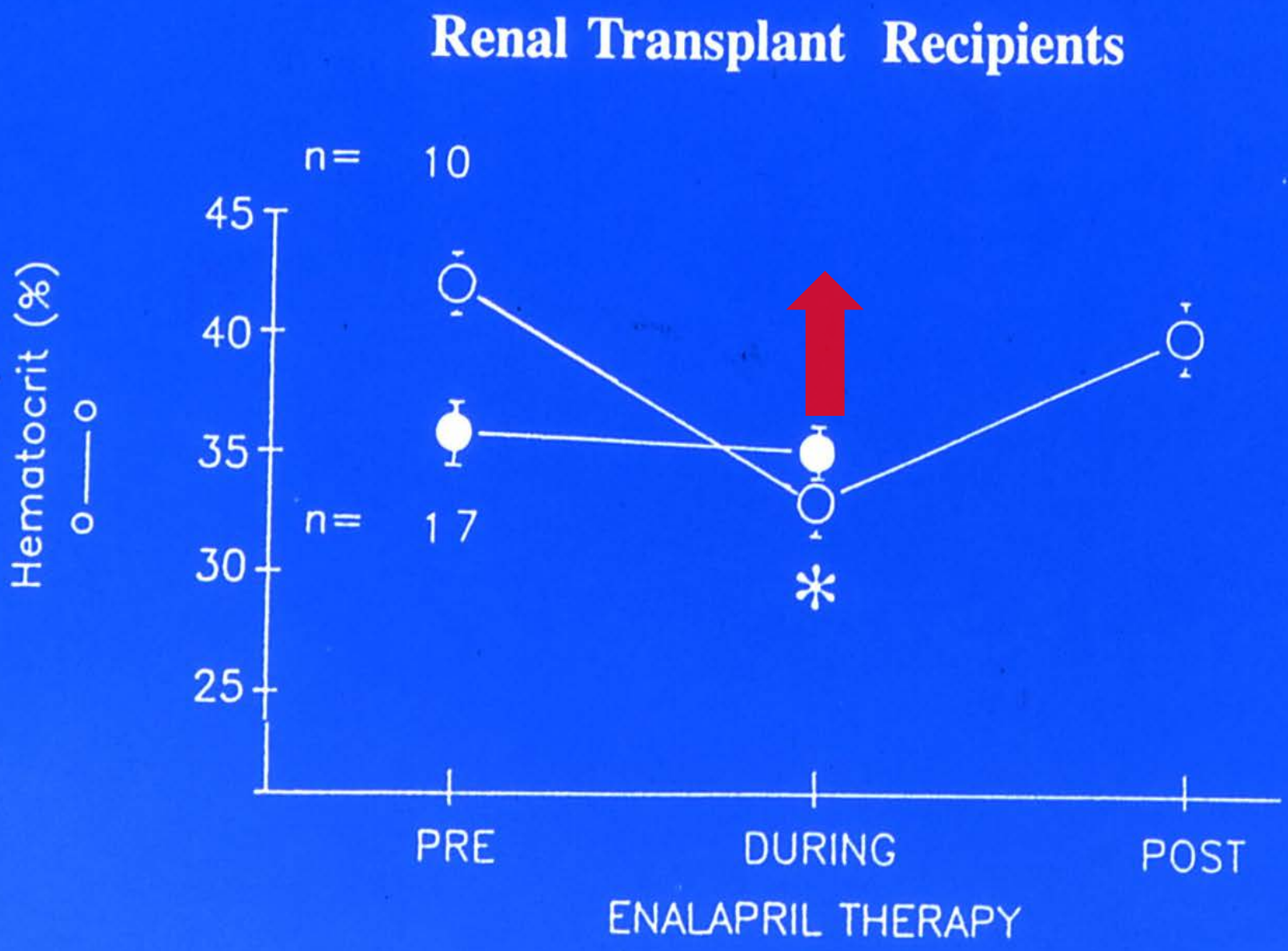
Το Σύστημα Ρενίνης-Αγγειοτασίνης και η ρύθμιση της Ερυθροποίησης

1) Κλινικές Παρατηρήσεις

Μεταμοσχευμένοι νεφροπαθείς



Vlahakos.....Madias, American Journal of Kidney Disease, 1991



Vlahakos..Madias, American Journal of Kidney Disease, 1991

MOURAD G, RIBSTEIN J, MIMRAN A. KIDNEY INT. 1993.

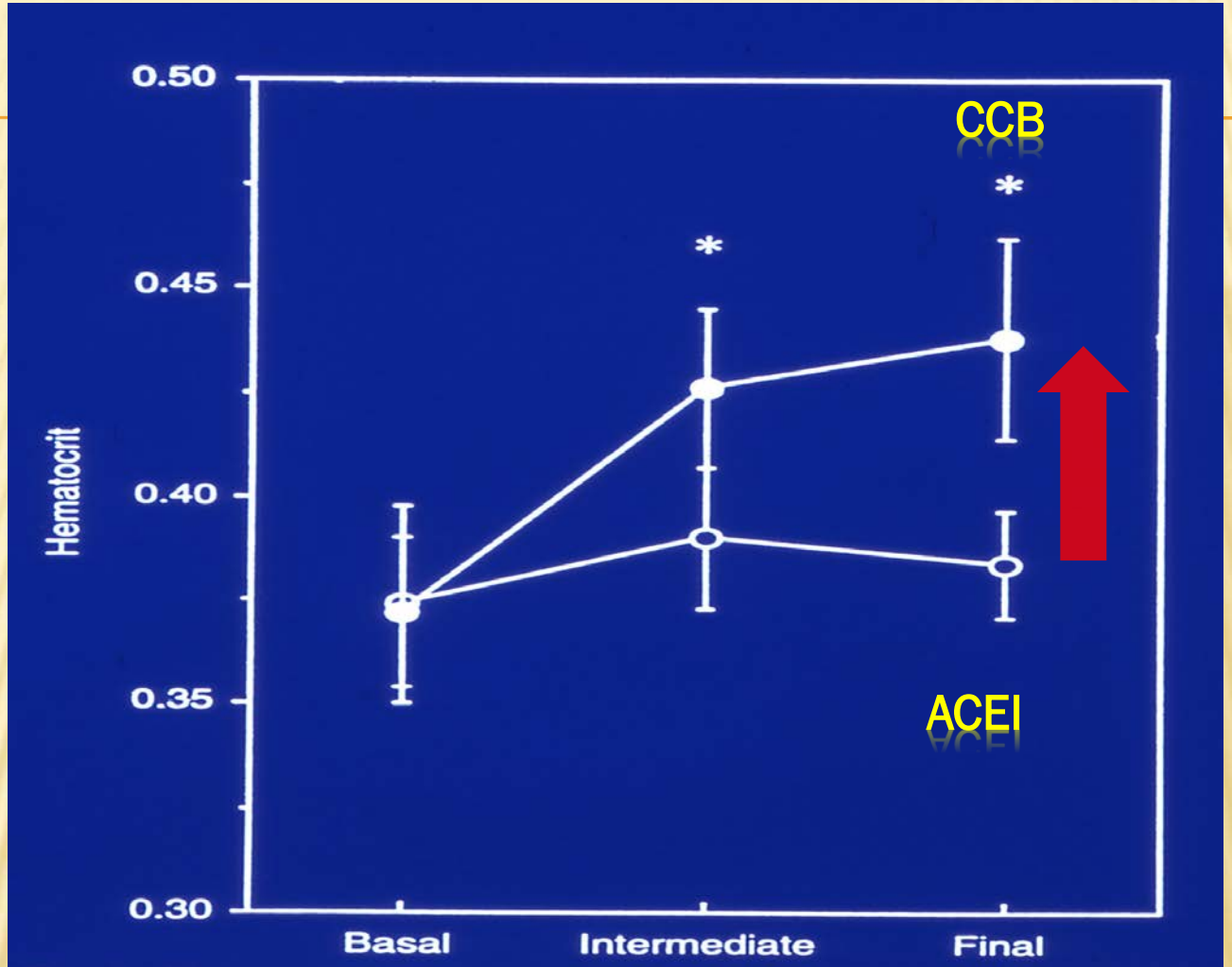
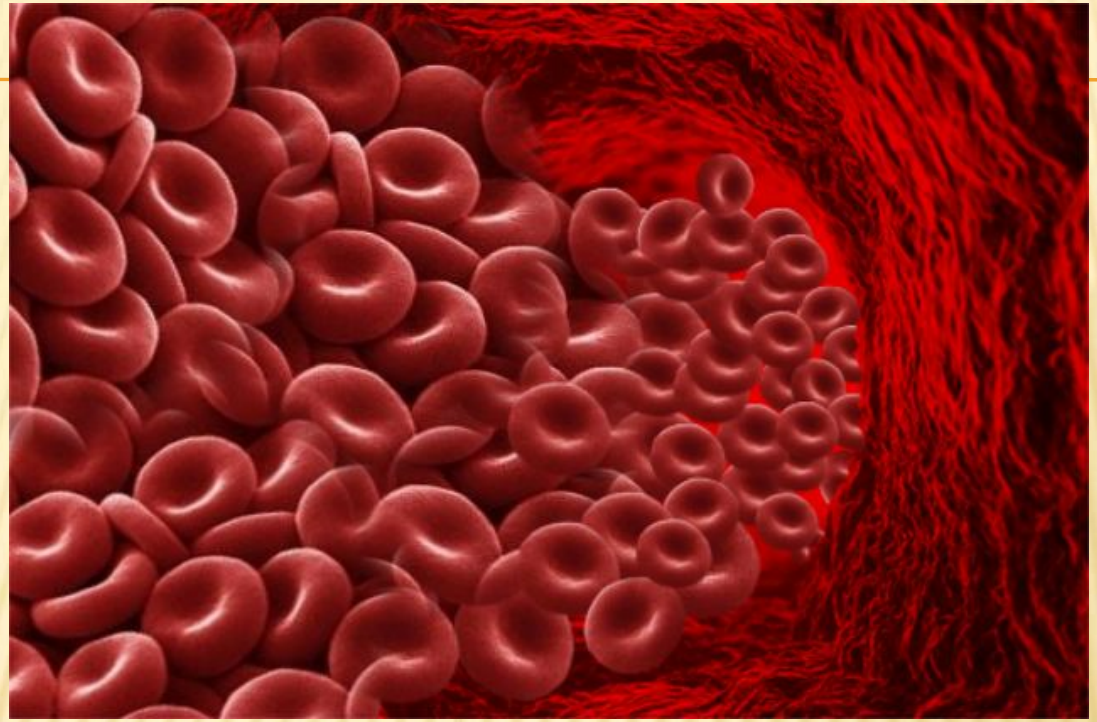


Fig. 2. *Changes in hematocrit associated with treatment by angiotensin-converting enzyme inhibitor (ACEI) or calcium antagonist (CA).* Intermediate study at about 1 year and final study at 2.5 years of follow-up respectively. *$P < 0.05$ when compared to the pretreatment values.

Mourad et al. 19

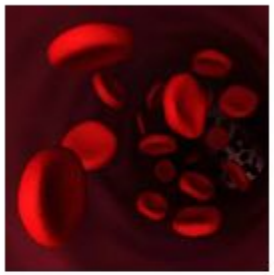


....we speculate that the hematocrit-lowering effect of RAS inhibition could be used for benefit in patients with erythrocytosis.

Vlahakos et al. American Journal of Kidney Disease 1991

POST-TRANSPLANT ERYTHROCYTOSIS

- Persistently elevated HgB/Hct following transplantation
- Hct >51% (HgB > 17)
- Occurs in 8-15% of renal transplant patients
- Typically occurs 8-24 months after transplantation.



Effects of Enalapril on Erythrocytosis after Renal Transplantation

Robert S. Gaston, MD; Bruce A. Julian, MD; Arnold G. Diethelm, MD; and John J. Curtis, MD

Annals of Internal Medicine. 1991;115:954-955.

Erythrocytosis afflicts 4% to 17% of renal allograft recipients. It appears most often within the first year after transplant, usually in patients with excellent graft function, and is associated with an increased risk for thromboembolic events (1). Although the pathophysiology is poorly defined, it may relate to excess production of erythropoietin by native kidneys (2). The standard therapy is serial phlebotomy (1), but no treatment has proved optimal. A recent report of enalapril-associated anemia in renal transplant recipients (3) led to a trial of this agent as therapy for post-transplant erythrocytosis.

Methods

Twelve renal allograft recipients (mean age, 39 ± 3 years) with an hematocrit greater than 0.52 on three consecutive outpatient visits were given enalapril. The starting doses were 2.5 to 5 mg/d, and were increased as necessary for blood pressure control. The elevated hematocrit had first been noted 8 ± 1 months (range,

From the University of Alabama Medical Center, Birmingham, Alabama. For current author addresses, see end of text.

(154 ± 10 and 153 ± 11 μmol/L) did not change. One patient, taking 5 mg/d, stopped enalapril on his own due to "dizziness" after 6 weeks (hypotension was not documented). A second recipient, whose hematocrit had declined from 0.60 to 0.56 after 2 months, experienced late rejection associated with tapering of cyclosporine. A third patient, with diabetes mellitus, contracted cryptococcosis (the hematocrit was 0.47 after 5 months). There have been no significant complications in the other nine patients.

After enalapril therapy was initiated, no patient required therapeutic phlebotomy. Two recipients who had previously had deep vein thromboses were taking war-

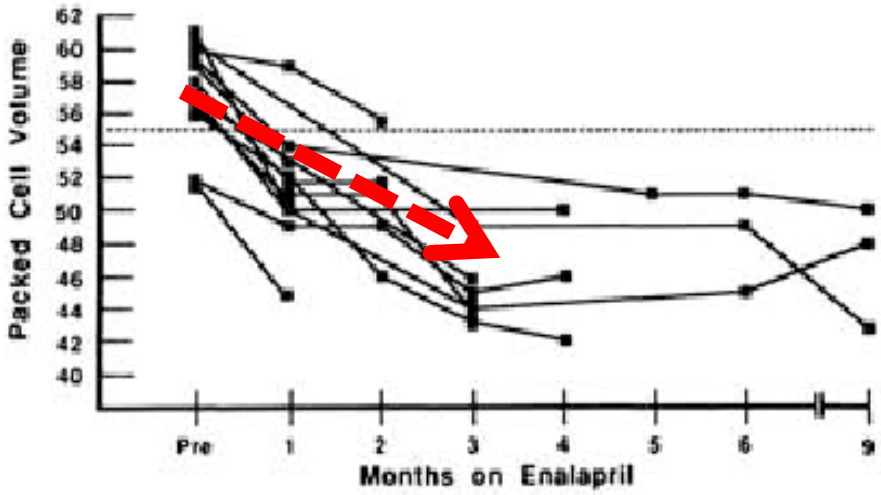


Figure 1. Hematocrit. The mean hematocrit (*packed cell volume*) is expressed as a percentage for 12 renal allograft recipients treated with enalapril, with length of follow-up in months. Values before enalapril was begun (*pre*) represent the mean hematocrit on three clinic visits immediately before therapy was started. The dotted line marks a hematocrit of 55%.

ERYTHROCYTOSIS FOLLOWING RENAL TRANSPLANTATION

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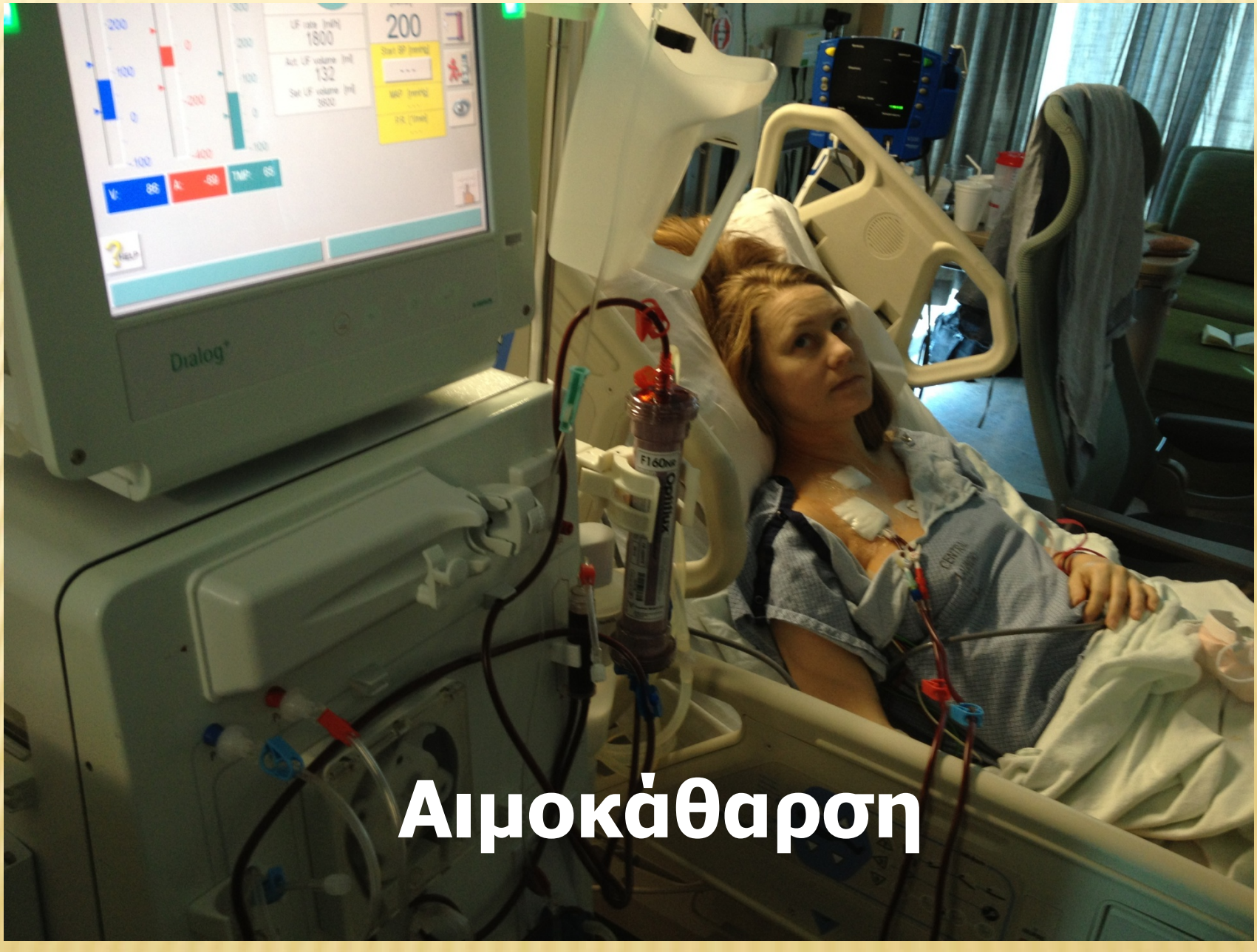
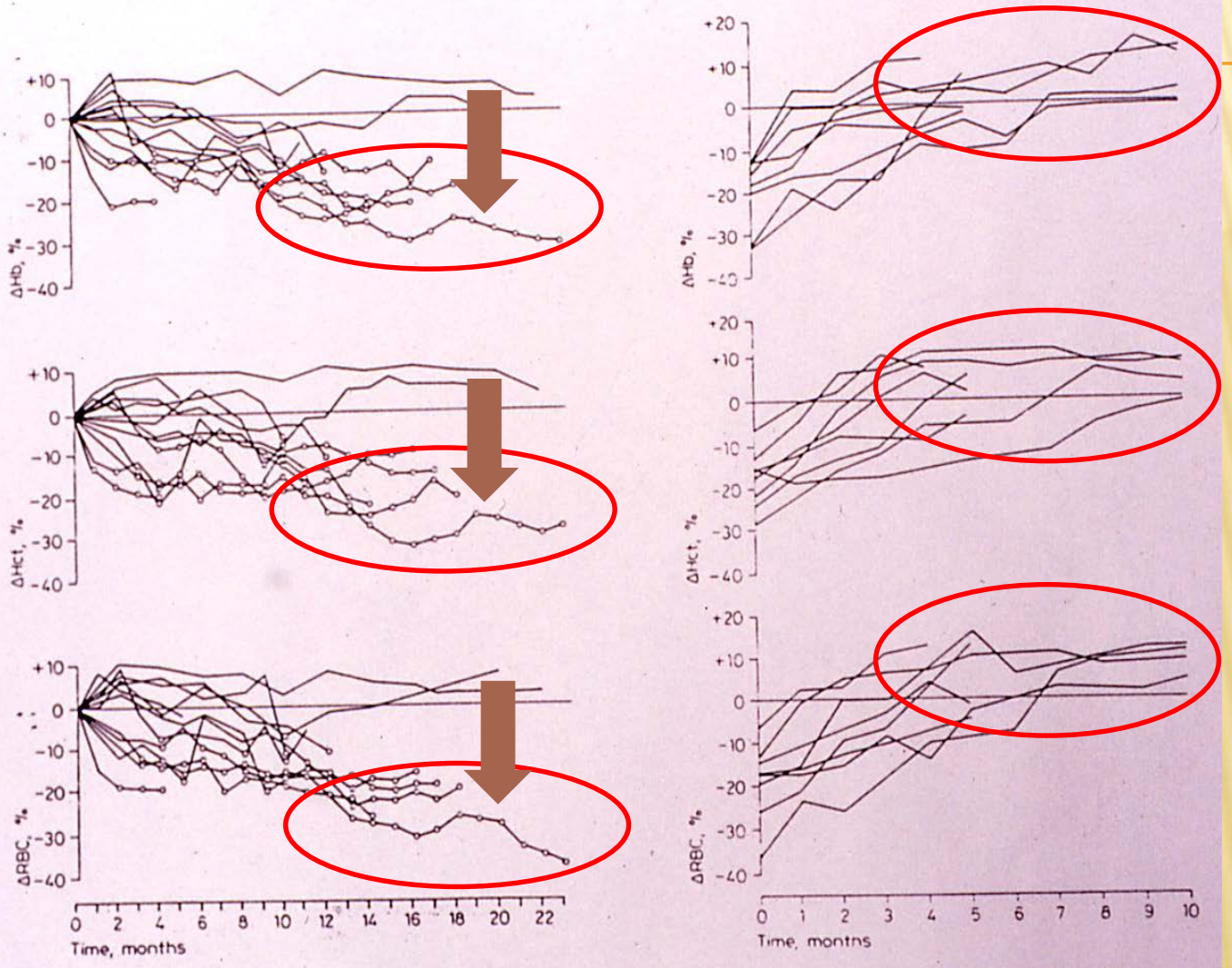


Αιμοκάθαρση

Hemodialysis Patients



+ Captopril **– Captopril**

Hirakata (1984)

Low Medium High Renin

Table 2. Predialysis laboratory data of chronic hemodialysis patients stratified according to predialysis renin levels[a]

Variable	Group A (n = 11)	Group B (n = 9)	Group C (n = 13)	P Value
PRA (ng.ml^{-1}.h^{-1})	0.37 ± 0.1	2.4 ± 0.2	12.9 ± 2.9	0.0001
Hematocrit (%)	30.1 ± 0.8	31.7 ± 1.0	31.8 ± 1.0	NS
BUN (mg/dl)	76 ± 4.4	79 ± 4.7	88 ± 5.5	NS
Albumin (g/dl)	3.9 ± 0.09	4.1 ± 0.11	4.2 ± 0.06	NS
Cholesterol (mg/dl)	204 ± 12	182 ± 13	211 ± 11	NS
Triglycerides (mg/dl)	195 ± 23	134 ± 22	223 ± 33	NS
Uric acid (mg/dl)	6.3 ± 0.3	6.9 ± 0.3	7.3 ± 0.5	NS
Glucose (mg/dl)	132 ± 16	115 ± 19	140 ± 13	NS
Sodium (mEq/L)	140 ± 0.7	141 ± 0.5	139 ± 0.7	NS
Potassium (mEq/L)	5.2 ± 0.1	4.8 ± 0.2	5.1 ± 0.2	NS
Calcium (mg/dl)	9.6 ± 0.16	9.7 ± 0.2	9.9 ± 0.17	NS
Phosphate (mg/dl)	4.7 ± 0.4	5.4 ± 0.4	4.9 ± 0.4	NS
PTH (pg/ml)	129 ± 20	168 ± 58	176 ± 26	NS

[a] PRA, plasma renin activity; BUN, blood urea nitrogen.

Vlahakos et al, J Am Soc Nephrol , 1997

Table 1. Demographic and clinical characteristics of chronic hemodialysis patients stratified according to predialysis renin levels[a]

Low **Medium** **High Renin**

Characteristic	Group A (n = 11)	Group B (n = 9)	Group C (n = 13)	P Value
Age	53.54 ± 4.4	44.7 ± 6.7	52.8 ± 3.6	NS
Gender (Male/Female)	6/5	7/2	12/1	NS
Body mass index (kg/m^2)	23.3 ± 0.9	22.6 ± 1.4	24.6 ± 1.2	NS
Blood pressure (mmHg)				
systolic	145.5 ± 4.8	149.4 ± 4.2	148.8 ± 4	NS
diastolic	75.0 ± 2.1	78.3 ± 1.9	80.8 ± 1.2	NS
mean	98.5 ± 2.8	102 ± 2.1	103.4 ± 1.9	NS
Heart rate (beats/min)	74.5 ± 1.6	80.6 ± 1	75.8 ± 2.1	NS
History of				
glomerulopathy	5 (45)	7 (78)	13 (100)	0.008
coronary artery disease	4 (36)	4 (44)	8 (61)	NS
diabetes mellitus	2 (18)	2 (22)	4 (30)	NS
smoking	4 (36)	4 (44)	5 (38)	NS
Medications				
antihypertensive	3 (27)	6 (66)	8 (61)	NS
rhEPO	9 (82)	6 (66)	1 (7)	0.0006
Interdialytic weight gain (kg)	2.17 ± 0.18	1.71 ± 0.3	2.33 ± 0.22	NS
Follow-up period on hemodialysis (mo)	39.8 ± 8.4	30.7 ± 4.2	37.8 ± 4.4	NS

[a] Numbers in parentheses indicate percentage of patients. rhEPO, recombinant human erythropoietin.

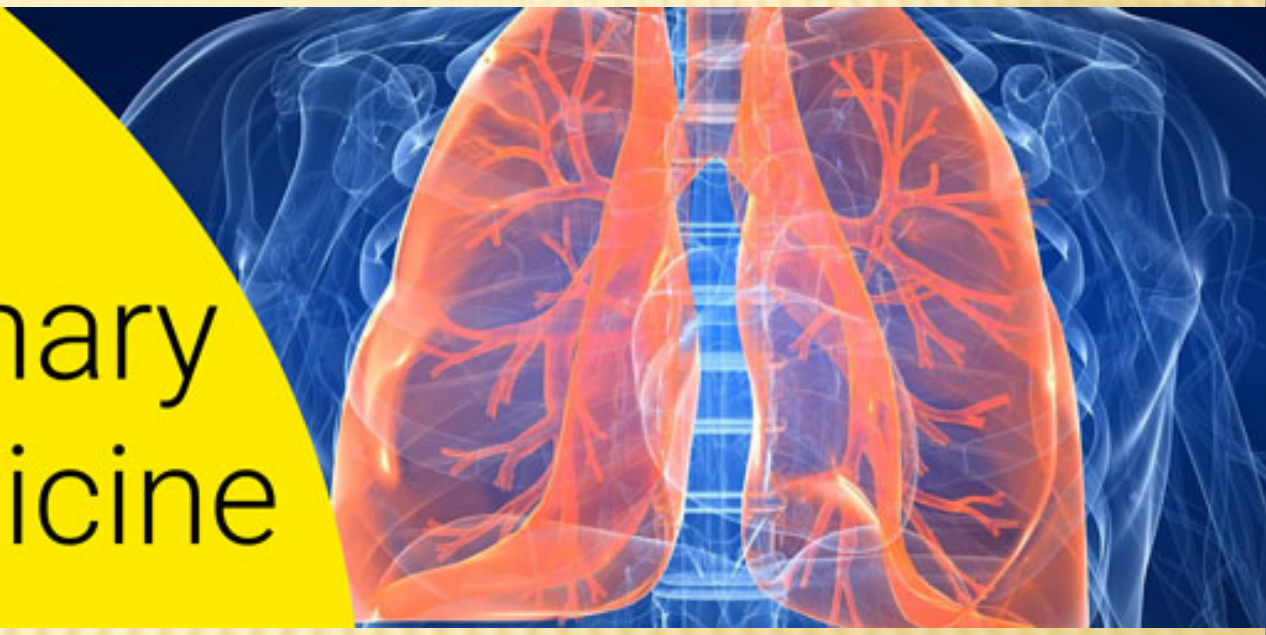
Vlahakos et al, J Am Soc Nephrol , 1997

Group	No. of Patients	Renin activity* (mμg %)	Erythropoietin activity* (% ^{59}Fe)
Control			
Saline	14		0.37 ± 0.03, $p < 0.001$
Normotensive subjects			
Normal	12	326 ± 22	0.60 ± 0.05
Chronic pulmonary disease	6	337 ± 32	0.80 ± 0.16
Anerythrocytogenic anemia	1	156	15.48
Hypertensive patients			
Nonrenovascular, nonaccelerated	8	323 ± 93	0.76 ± 0.08
Renovascular, nonaccelerated	11	1,498 ± 492, $p < 0.025$	1.52 ± 0.21, $p < 0.001$
Nonrenovascular, accelerated	6	928 ± 154, $p < 0.001$	0.52 ± 0.22
Renovascular, accelerated	8	2,391 ± 496, $p < 0.001$	1.66 ± 0.43, $p < 0.01$

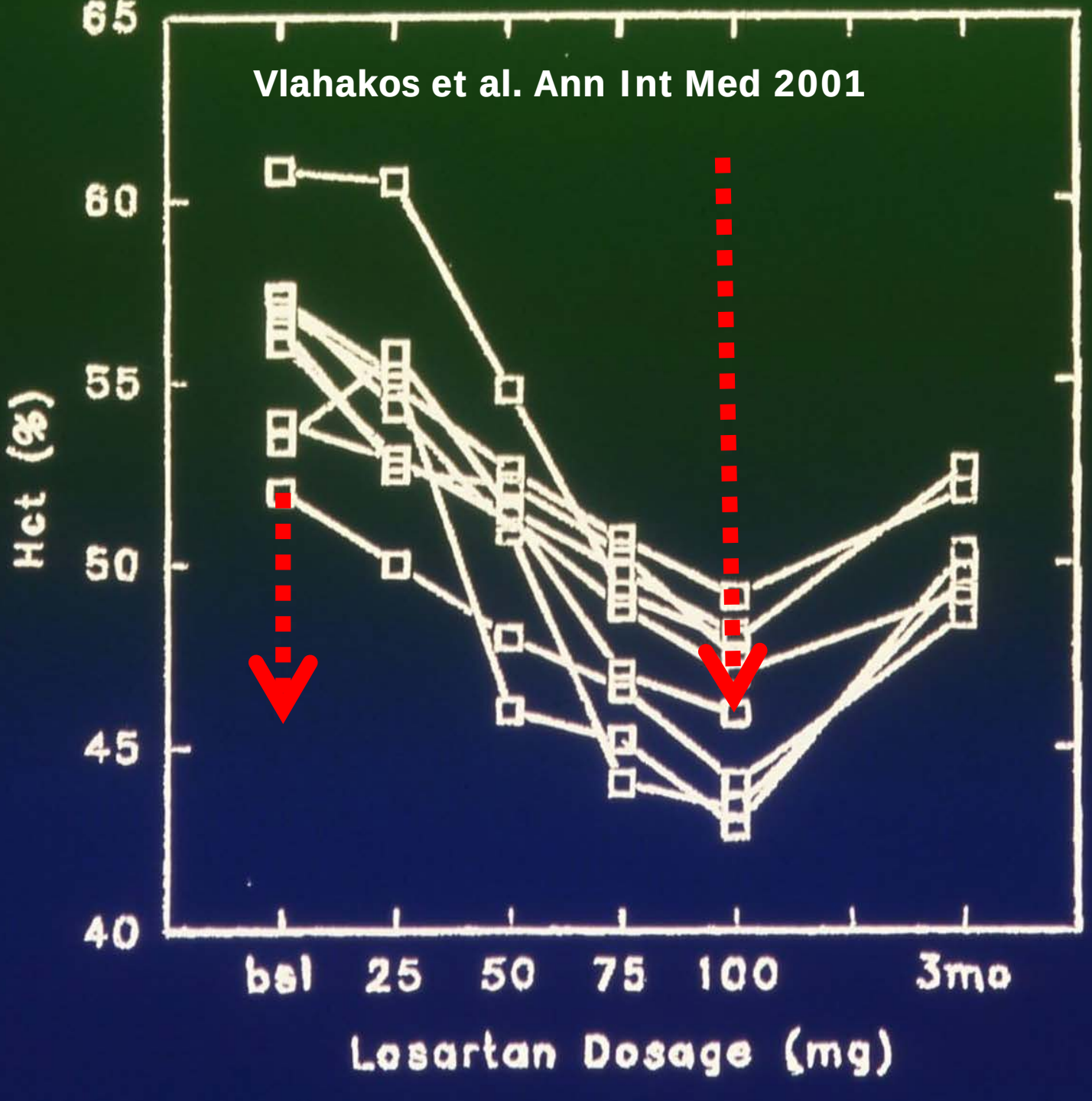
*Activities are given as means ± standard errors. A p value refers to the significance of a difference between the mean for the normal subjects and the mean for a group of patients; only p values less than 0.05 are cited.

Bourgoignie et al., 1968

Pulmonary Medicine



Vlahakos et al. Ann Int Med 2001

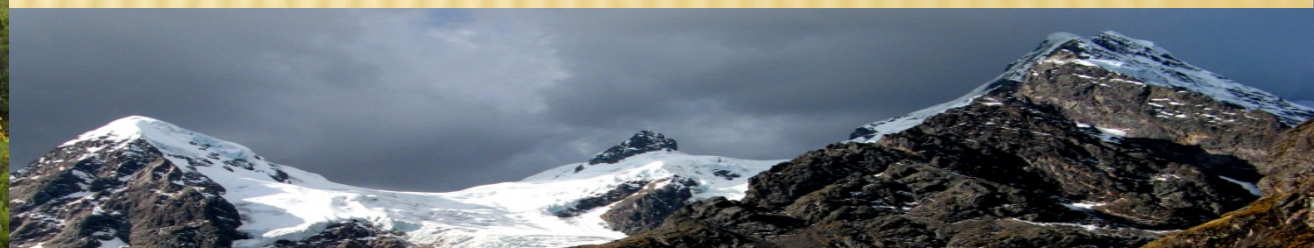


	Study Group (enalapril 5 mg qd) N=13			Control Group N=13		
	Baseline	1 year	2 years	Baseline	1 year	2 years
SBP (mmHg)	126	124	124	113	120	122
DBP (mmHg)	80	78	78	75	77	76
Hct (%)	64	60	57	60	60	59
		106	106	97	106	106
		285	248	250	289	298

-7%

-1%

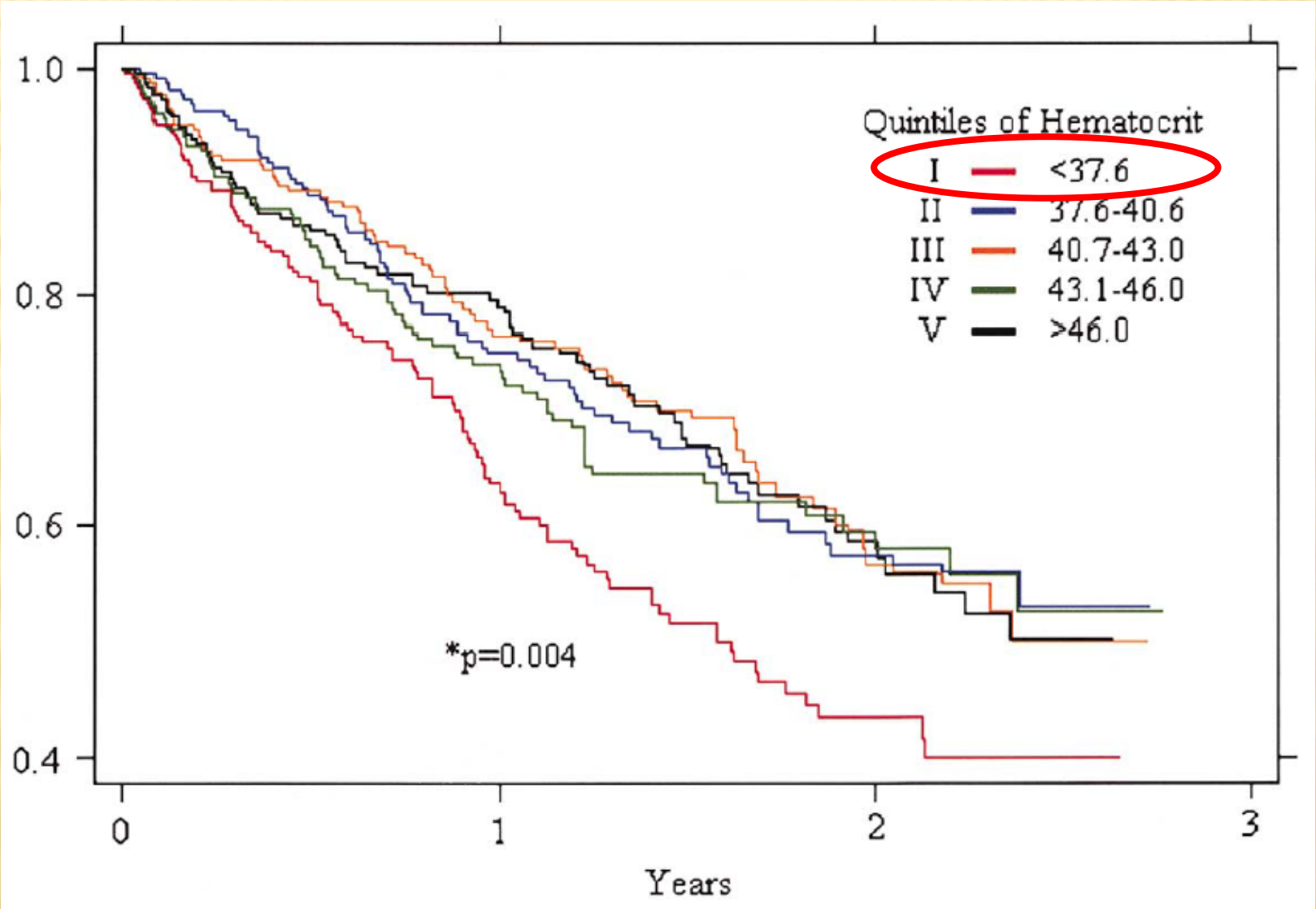
Plata et al., Lancet 2002;359:663-666



ΚΑΡΔΙΑΚΗ ΑΝΕΠΑΡΚΕΙΑ

ANEMIA PREDICTS MORTALITY IN SEVERE HEART FAILURE (PRAISE)

JACC 2003;41:1933



, for analyses of new anemia at one year, we luals to have complete data at one year; this exclusion of 1,075 patients. Consequently, ncluded 4,174 patients (analyses of new justment for data at one year), 5,249 patients ew anemia with adjustment for data at , or 6,436 individuals (analyses of prevalent ia and all survival analyses) (Fig. 1). The teristics of those included in our main anal- ed that there were no significant differences

Enalapril and the odds of developing new anemia at one year. At one year after randomization, 11.3% of those randomized to enalapril had developed new anemia, compared to 7.9% of those assigned to placebo (unadjusted odds ratio [OR] 1.48, 95% confidence interval [CI] 1.20 to 1.82). In a logistic model (Table 2) with adjustment for confounders, enalapril continued to be associated with new anemia at one year (adjusted OR 1.56, 95% CI 1.26 to 1.93). A potential confounder of this analysis was that individuals randomized to enalapril had greater changes in creatinine

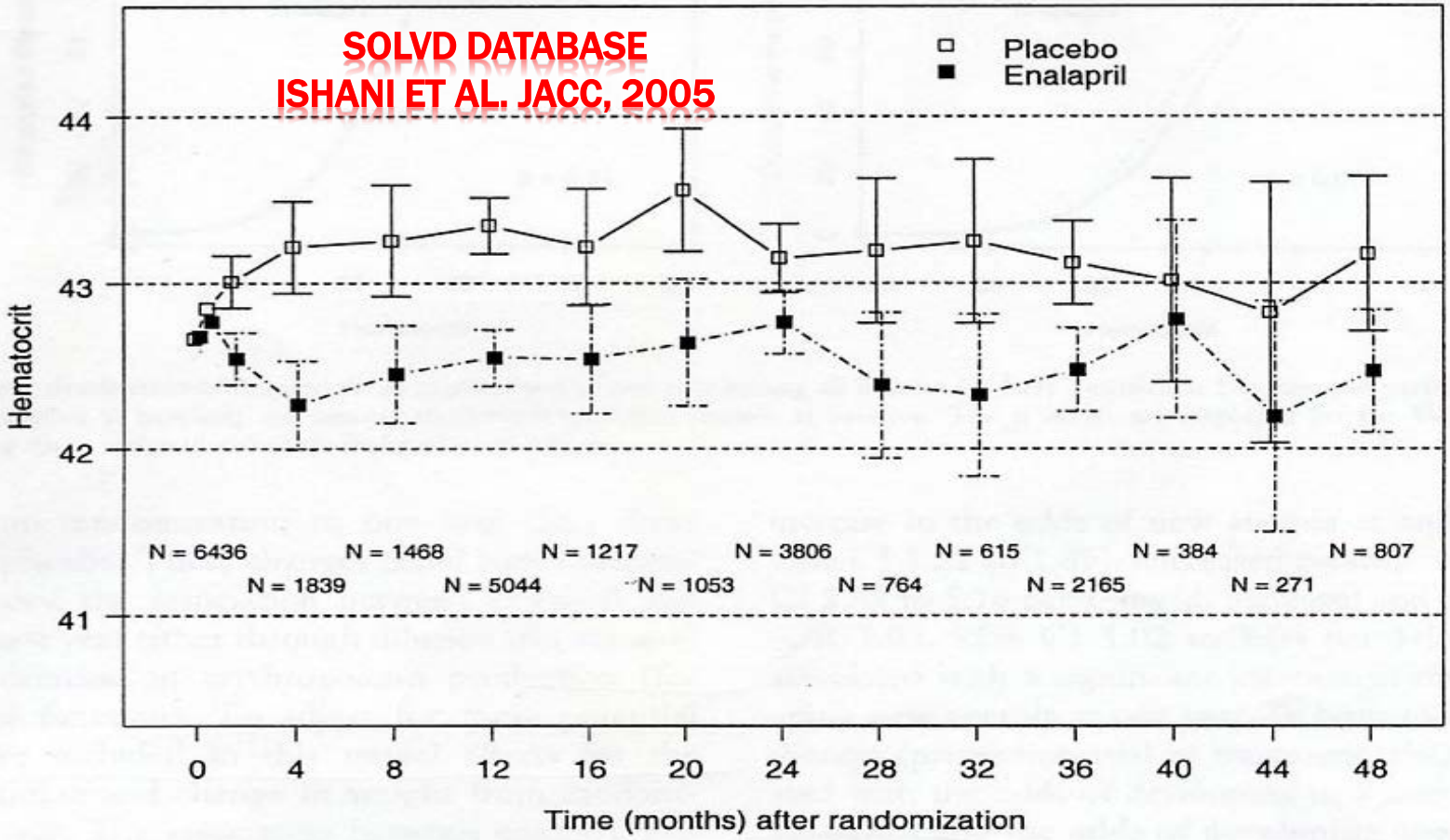


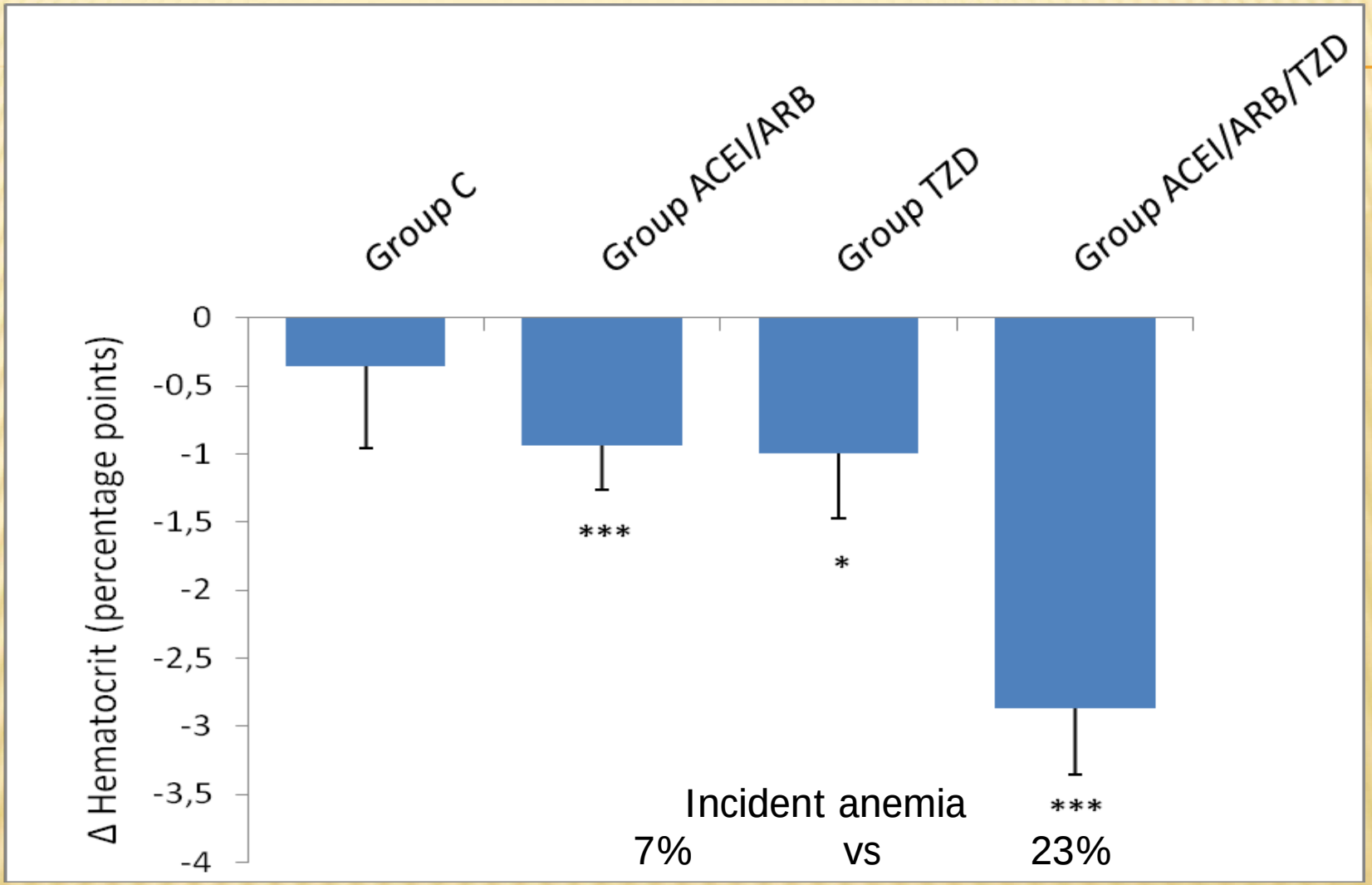
Table 5: The difference in Hb level between patients on ACEIs and patients who are not is significant.

	ACEI users	95% Confidence Interval	Non ACEI users	95% Confidence Interval
Mean	122.69	116.87 - 128.52	139.23	135.51 - 142.94
Standard Deviation	17.96		14.00	
Standard Error of Mean	2.88		1.85	
Number of patients	39		57	

The two-tailed P value is less than 0.0001, t=5.06, df=94

Table 2: Multinomial logistic regression shows the relative risk (RR) of various risk factors for the development of anaemia among patients with CHF.

	RR	Std Err.	Z	P value	95% Confidence Interval
ACEI	17.38	20.00	2.48	0.013	1.82 - 165.9
Aspirin	2.65	1.97	1.32	0.187	0.62 - 11.33
Renal impairment	2.16	1.57	1.06	0.288	0.52 - 8.95
65 years or more	0.96	0.77	-0.05	0.959	0.20 - 4.66
Gender	0.78	0.55	-0.35	0.727	0.20 - 3.13



A. RAPTIS , ...D. VLAHAKOS, EXP CLIN ENDOCRINOL DIABETES. 2012

QJM. 2015, 108(11):879-84.

RENIN-ANGIOTENSIN SYSTEM INHIBITORS LINKED TO ANEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS.

CHEUNGPASITPORN ET AL.

- Seven studies (2 cohort and 5 cross-sectional studies) with **29,061 patients** were included
- The pooled **RR of anemia in patients receiving ACEIs was 1.56** (95% CI, 1.40-1.73, I(2) = 17%).
- The pooled **RR of anemia in patients receiving ARBs was 1.60** (95% CI, 1.27-2.00, I(2) = 39%).

- **CONCLUSIONS:**

  Our meta-analysis demonstrates an association between anemia and the use of RAS inhibitors. Hematological parameters should be monitored in patients treated with RAS inhibitors

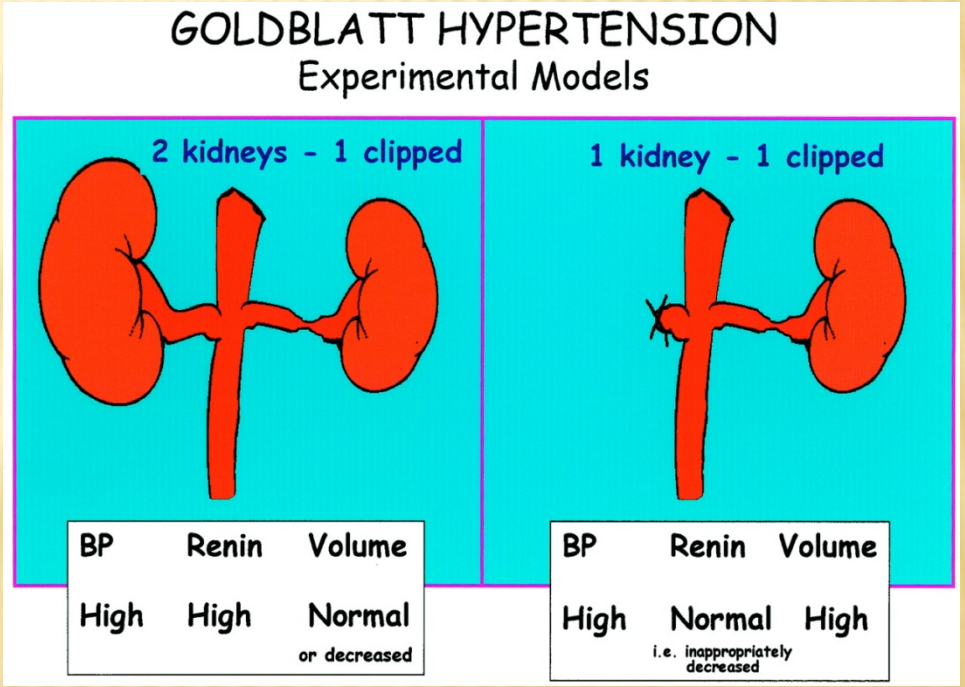
Το Σύστημα Ρενίνης-Αγγειοτασίνης και η ρύθμιση της Ερυθροποίησης

2) Πειραματόζωα

EXPERIMENTAL OBSERVATIONS

- Increased hematocrits were reported in the 1C-2K Goldblatt model of renin-dependent hypertension.

Harry Goldblatt
(1891-1977)



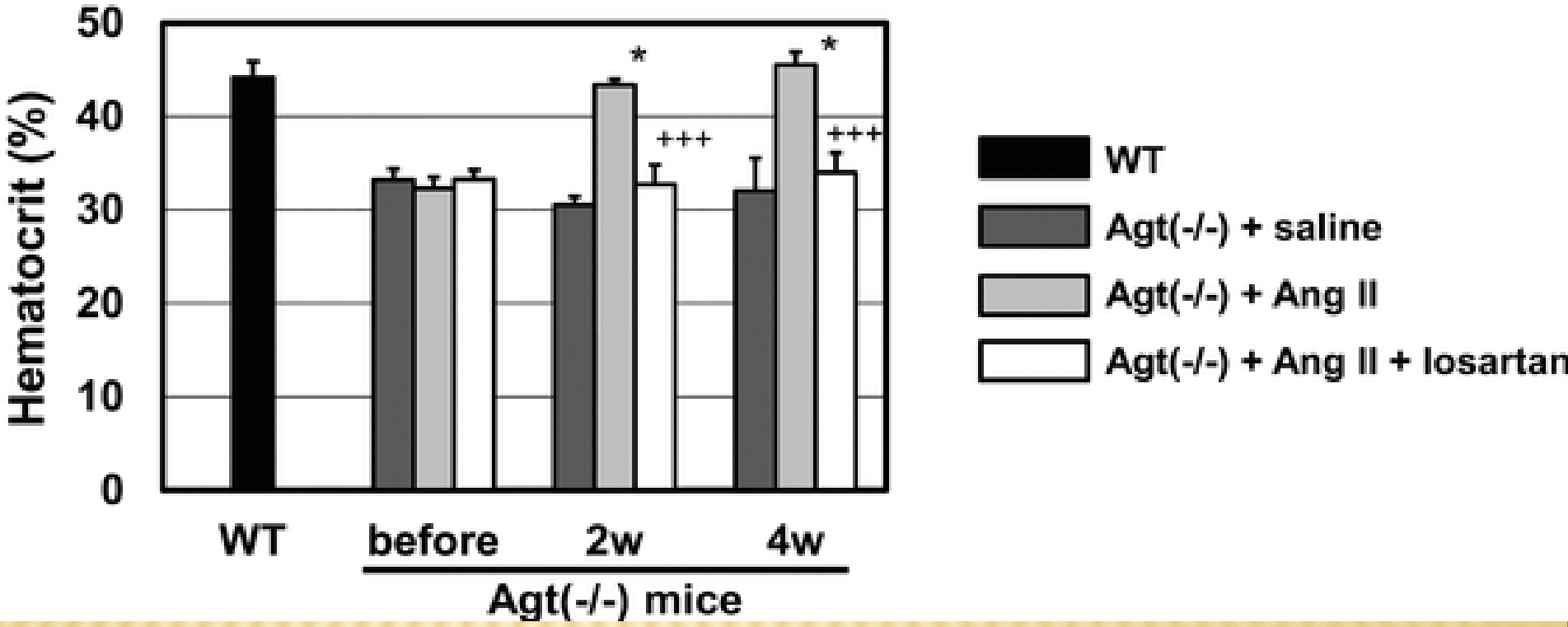
TRANSGENIC MICE

- Development of hypertension is accompanied by persistently **increased hematocrits** in transgenic mice that carried both

  the **human renin and angiotensinogen genes.**
- Both blood pressure and hematocrit remained normal when the 2 transgenes were introduced into the **AT1- receptor null** background, an observation that highlights the pivotal role of the AT1 receptor.

Kato et al. FASEB 2005

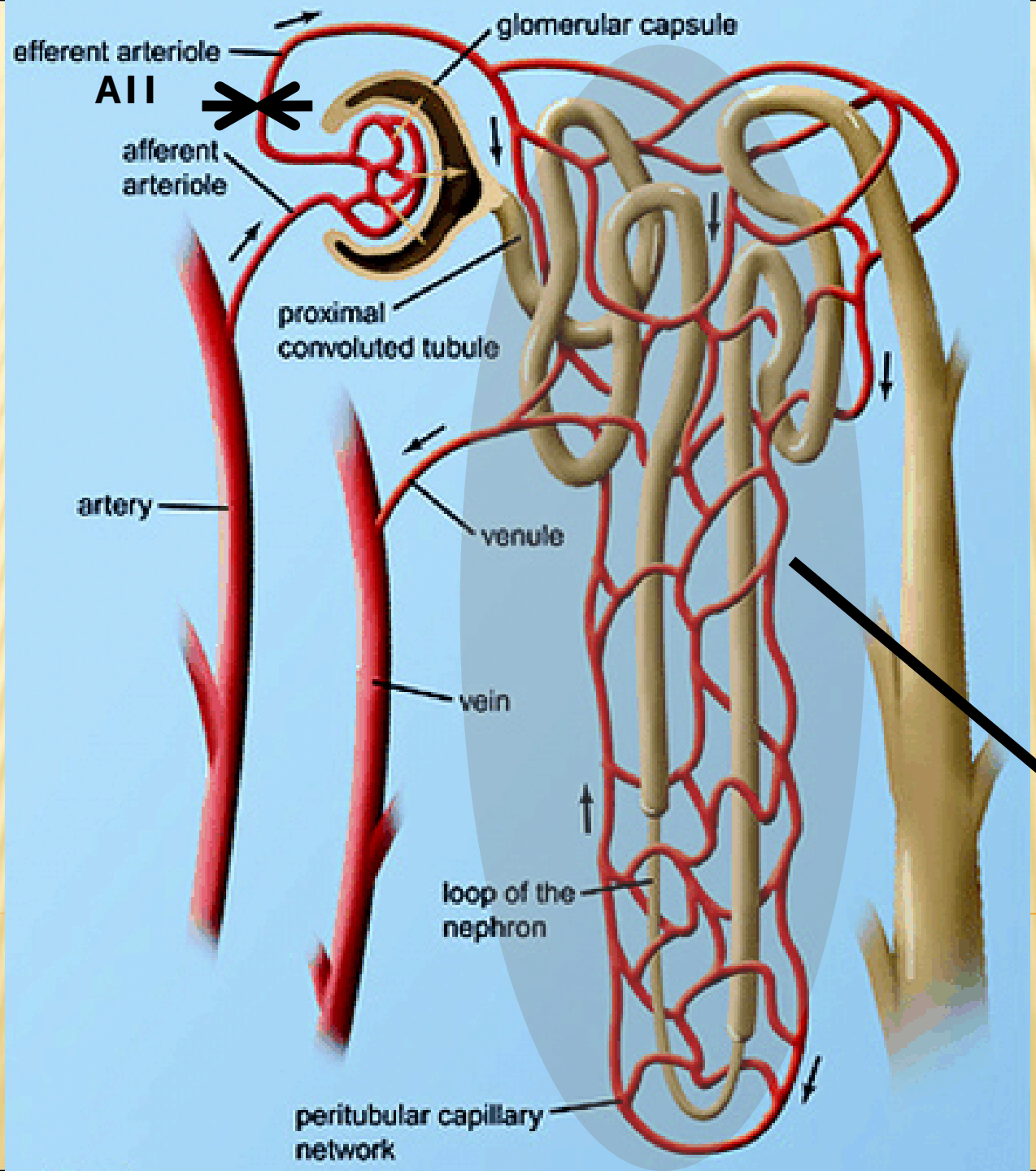
Fig 3. Systolic blood pressure and hematocrit values in Agt(-/-) mice after chronic administration of Ang II, with or without oral administration of losartan.



Kato et al. 2015

PLOS ONE

ΠΑΘΟΦΥΣΙΟΛΟΓΙΚΟΙ ΜΗΧΑΝΙΣΜΟΙ


efferent arteriole
AII
glomerular capsule
afferent arteriole
proximal convoluted tubule
artery
venule
vein
loop of the nephron
peritubular capillary network
EPO

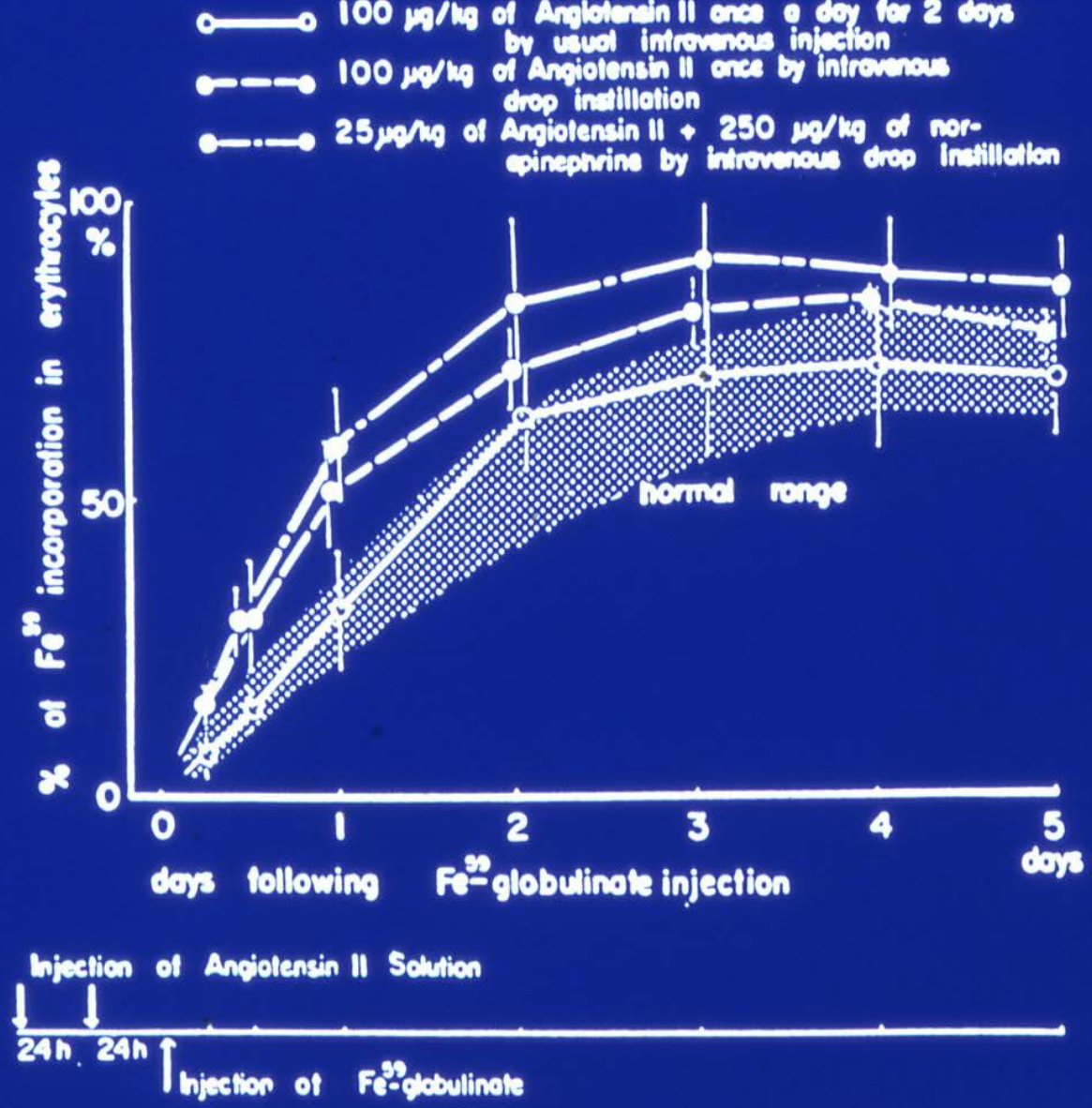
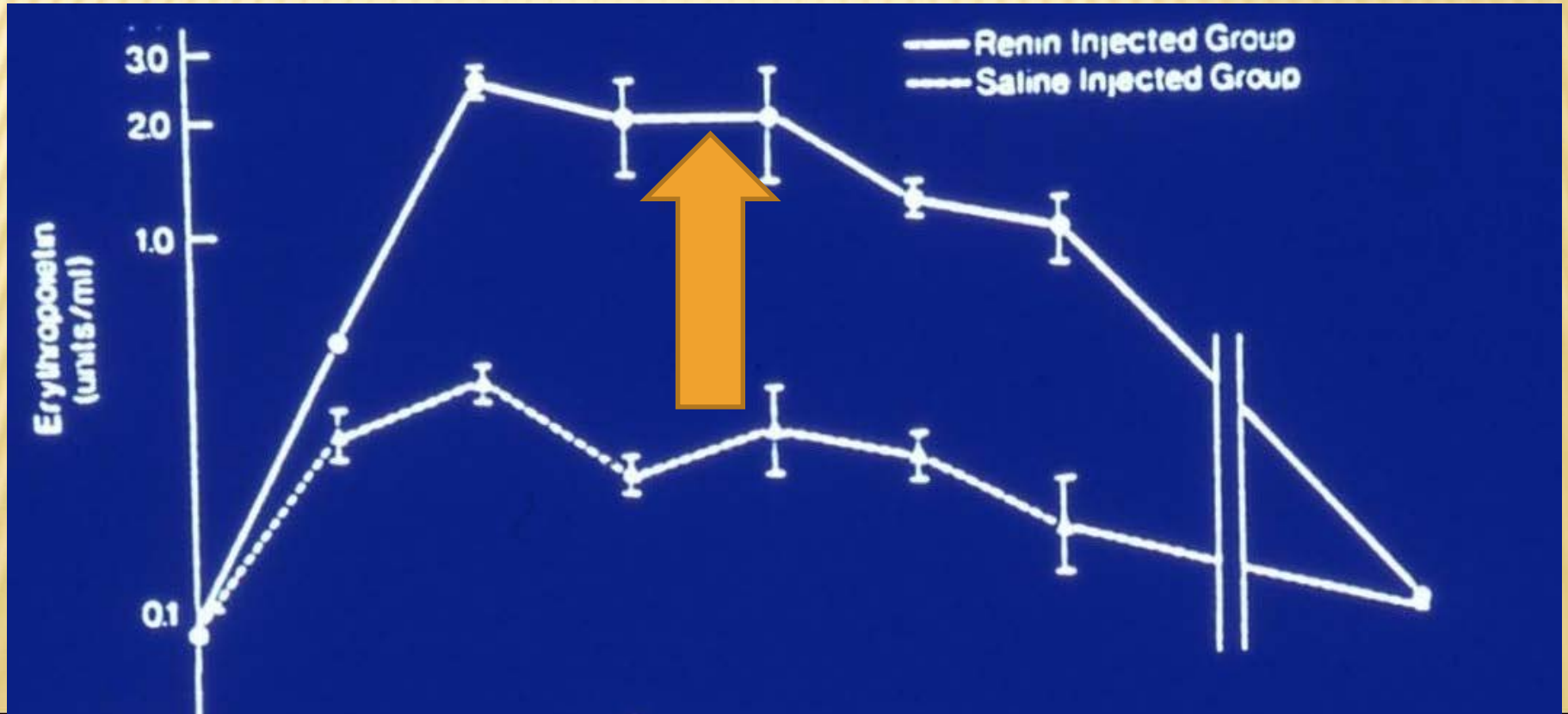


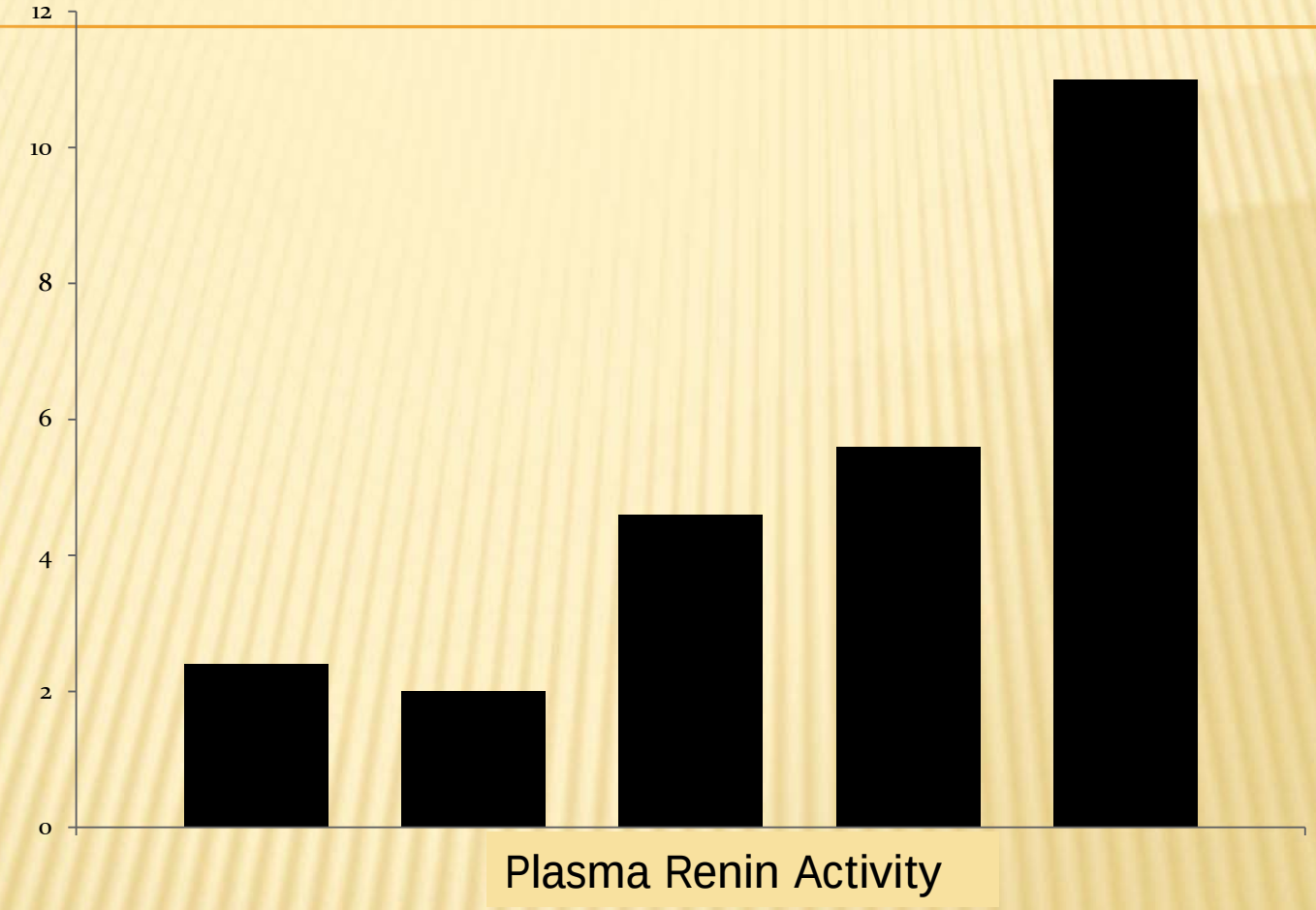
Fig. 1.—Effects of Angiotensin II injection on erythropoiesis in rabbits.

Nakao et al. 1967

GOULD ET AL. 1973



VOLPE ET AL. AM J CARDIOL 1994



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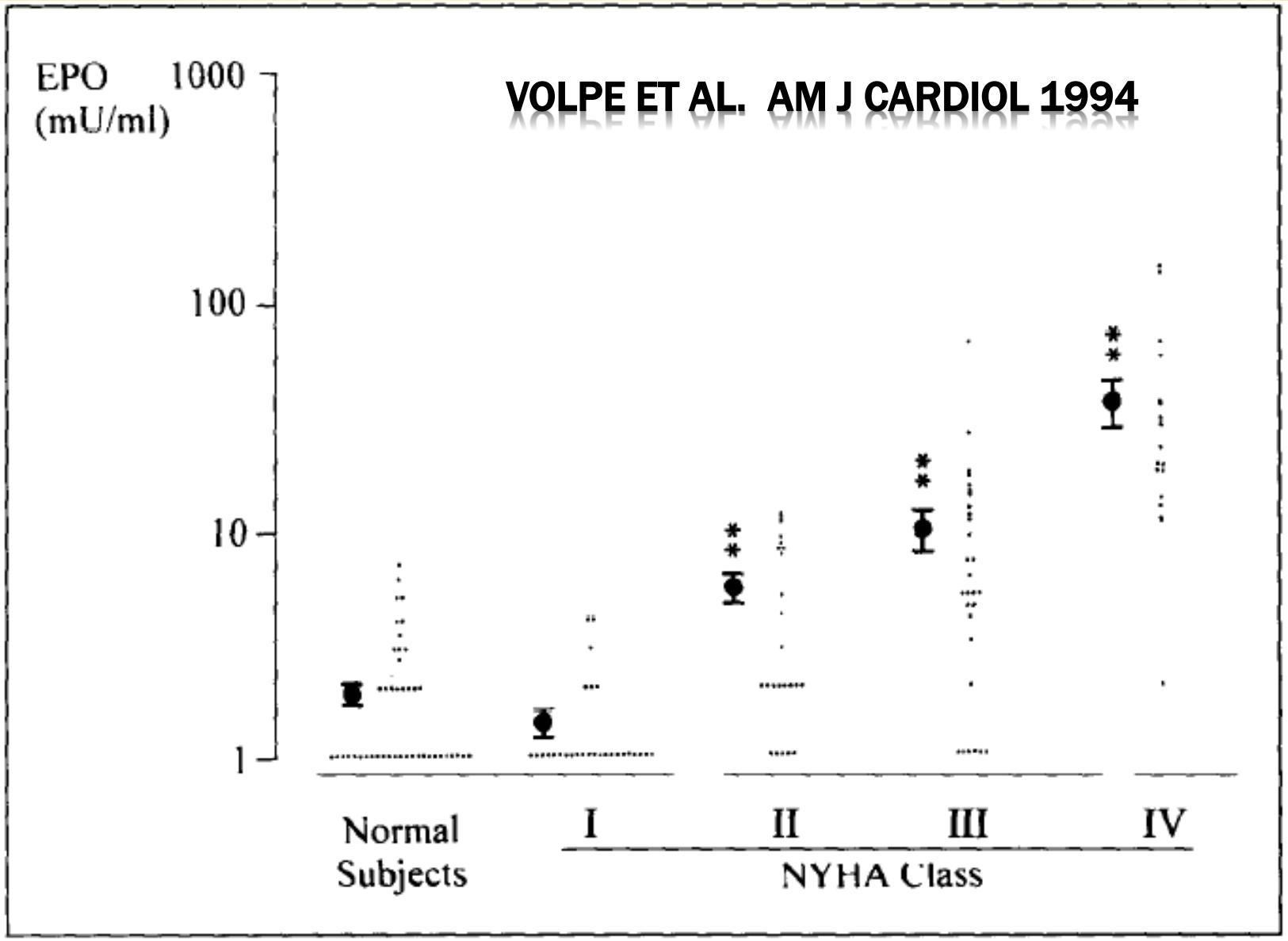

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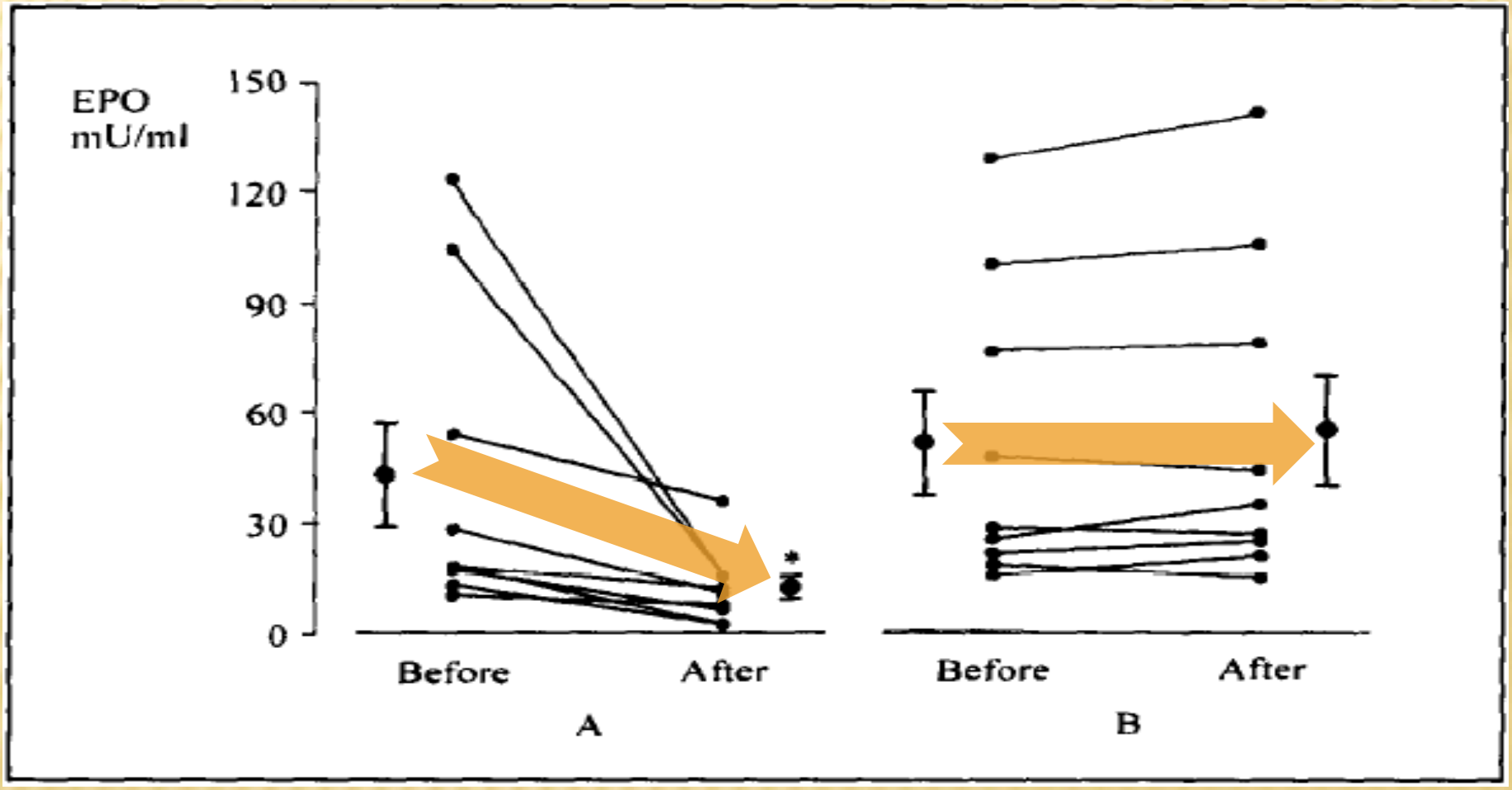
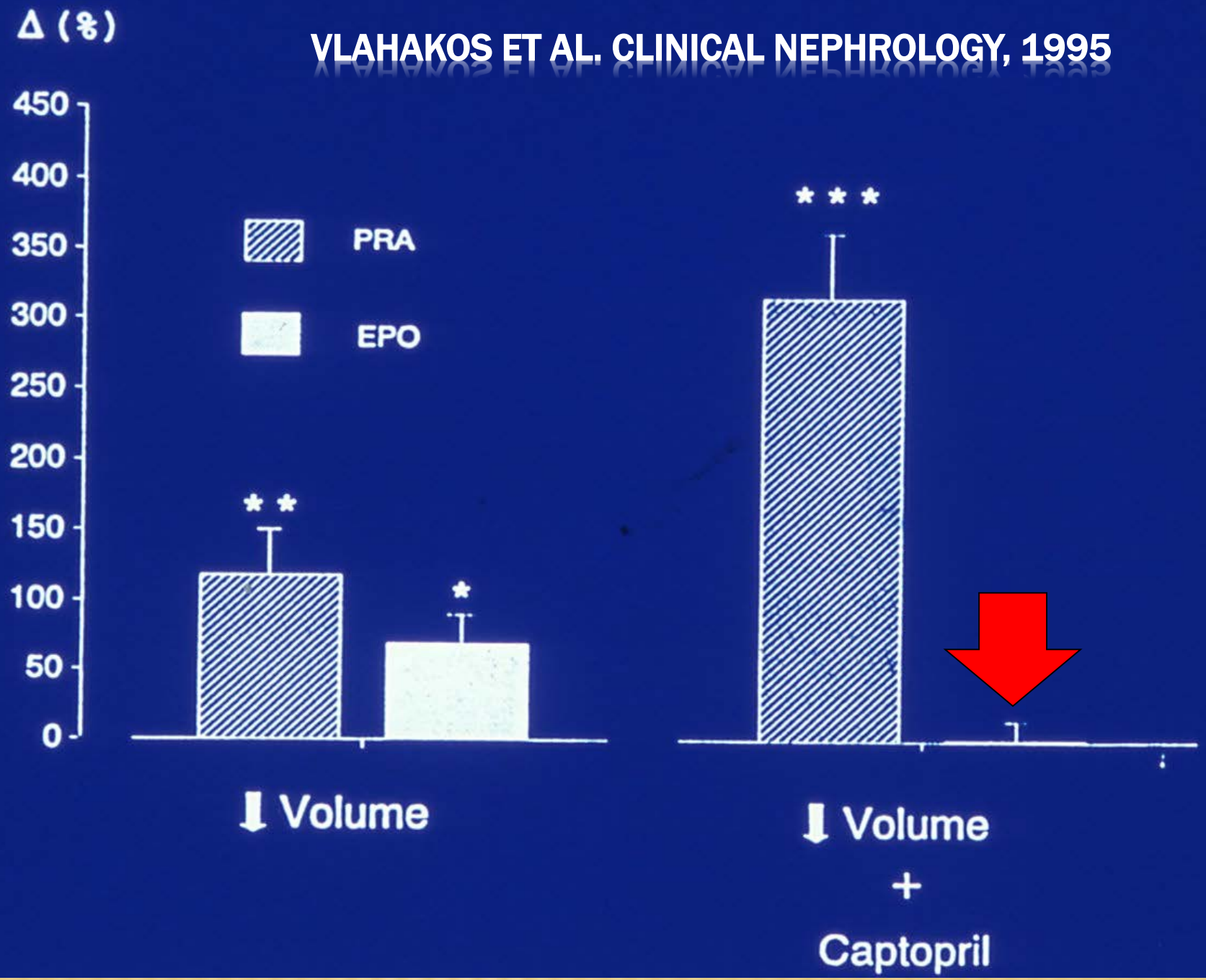


VLAHAKOS ET AL. CLINICAL NEPHROLOGY, 1995



Gossmann et al, KI 2001

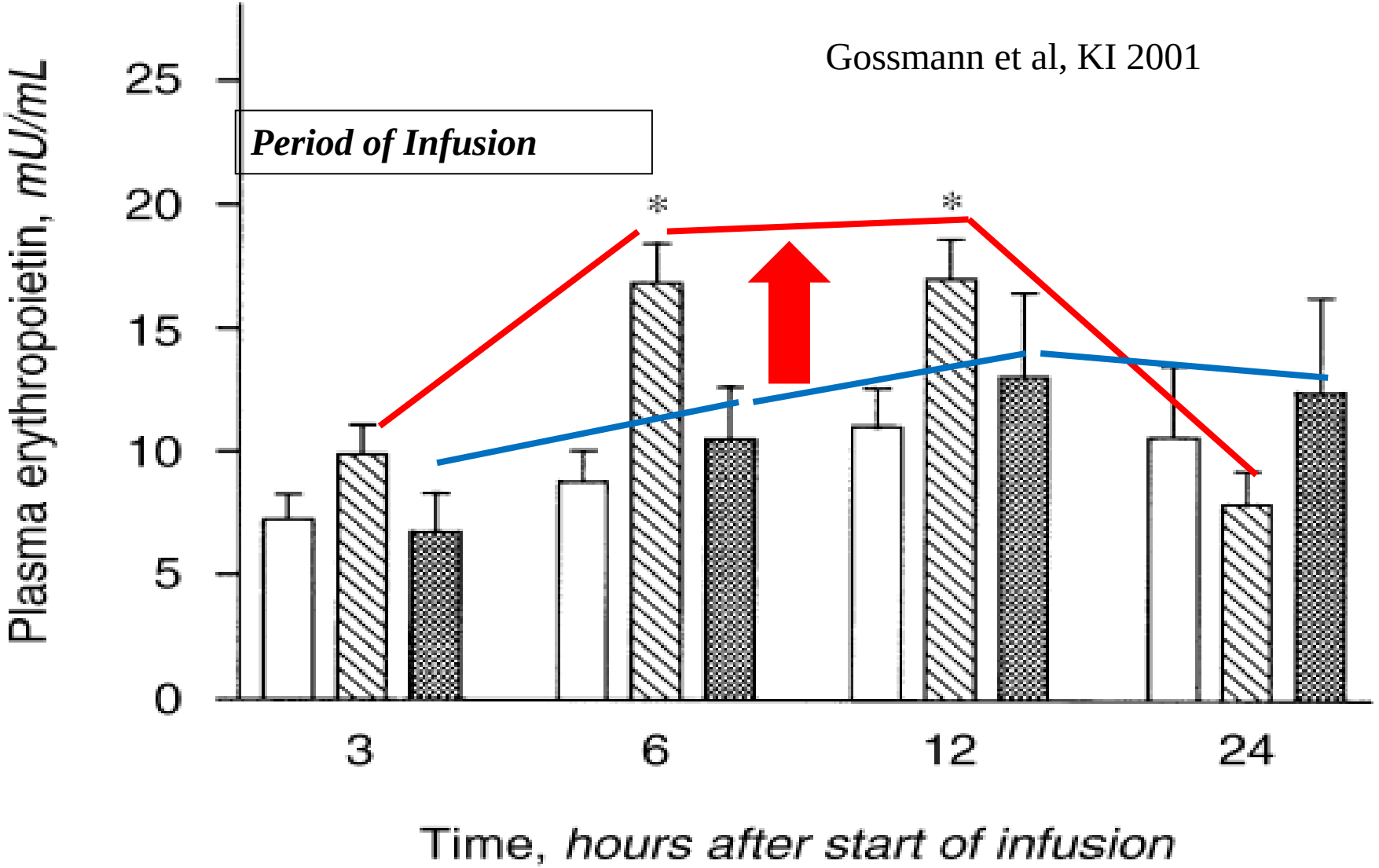


Fig. 2. Erythropoietin (EPO) plasma levels in healthy volunteers following a six-hour placebo or Ang II infusion without and with pretreatment with valsartan, an AT_1R blocker. Symbols are: (□) placebo; (▨) Ang II; (▩) Ang II + valsartan; *P = 0.01 vs. placebo. Data are represented as mean ± SEM.

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Posttransplant erythrocytosis

Demetrios V. Vlahakos, Katerina P. Marathias, Basil Agroyannis, and Nicolaos E. Madias

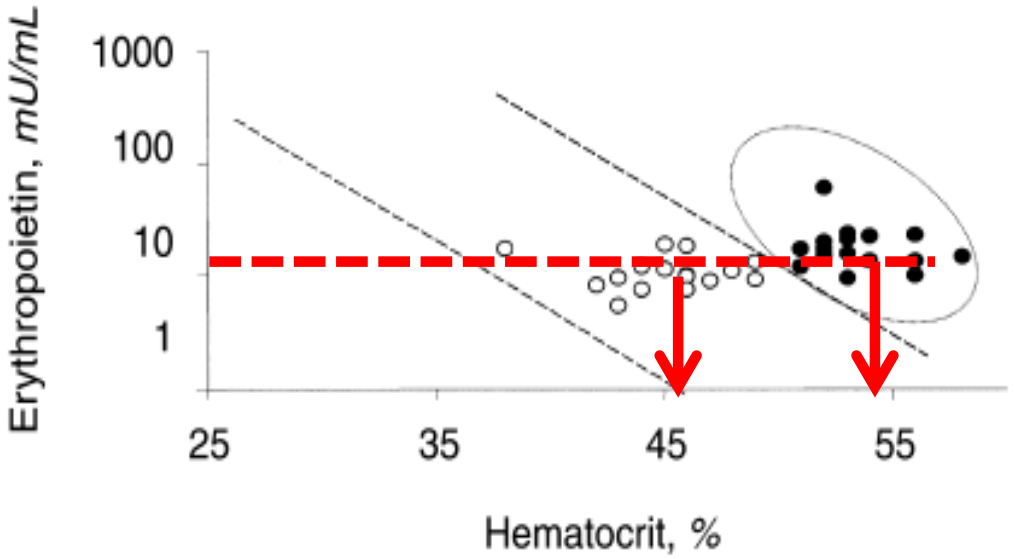
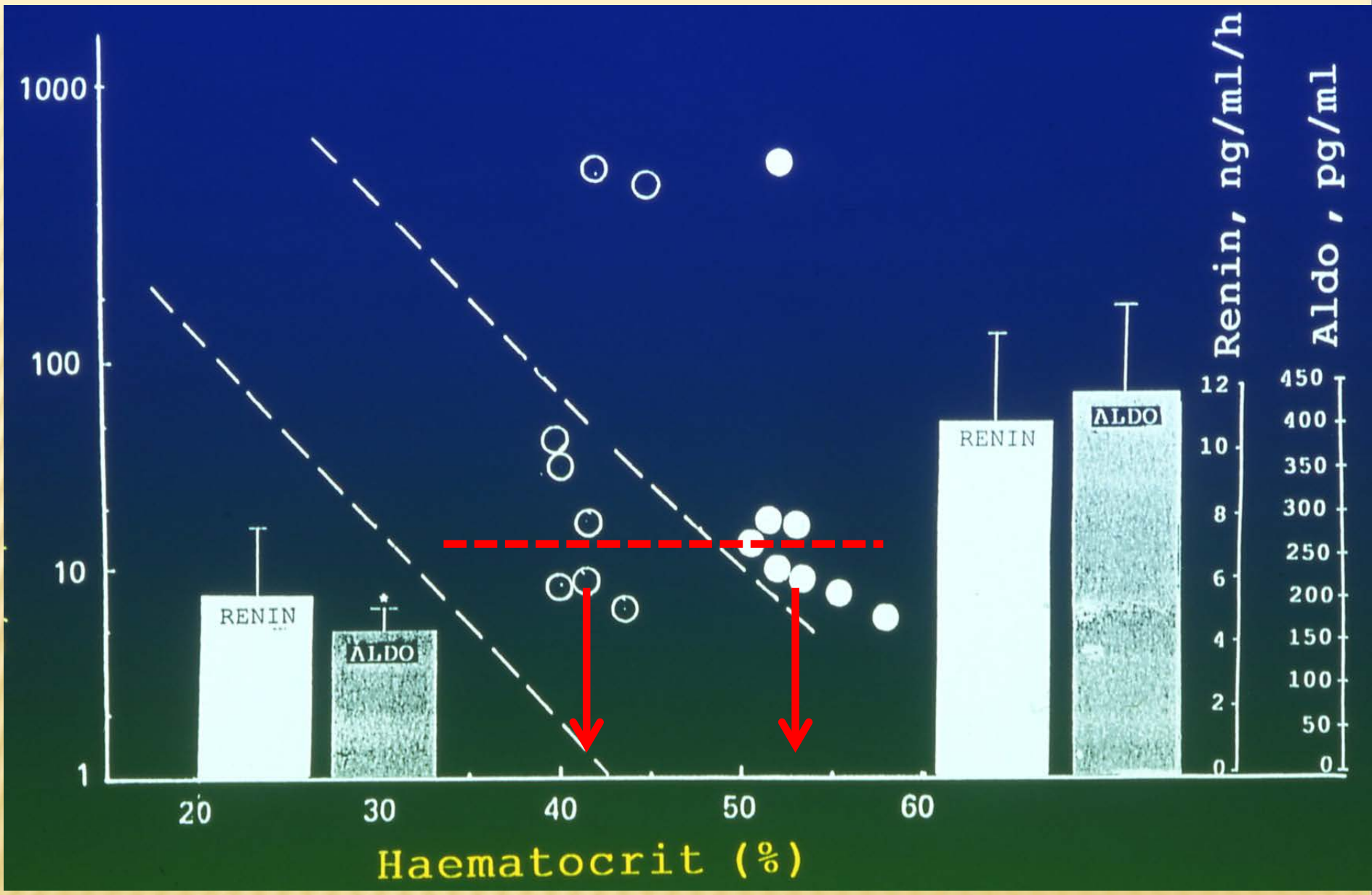


Fig. 2. Relationship of mean plasma erythropoietin levels and hematocrit determinations in published series on posttransplant erythrocytosis (PTE) (Table 1). The dashed lines represent the 95% confidence limits for nonuremic individuals [1]. The erythropoietin/hematocrit relationship in untreated patients with PTE (closed circles within the oval perigram) is shifted to the right due to inappropriately sustained erythropoietin secretion despite erythrocytosis (a form of "tertiary hypererythopoietinemia"). After treatment with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II AT1 receptor antagonist, the erythropoietin/hematocrit relationship returns within the normal limits (open circles).



Vlahakos et al. Am J Med , 1999

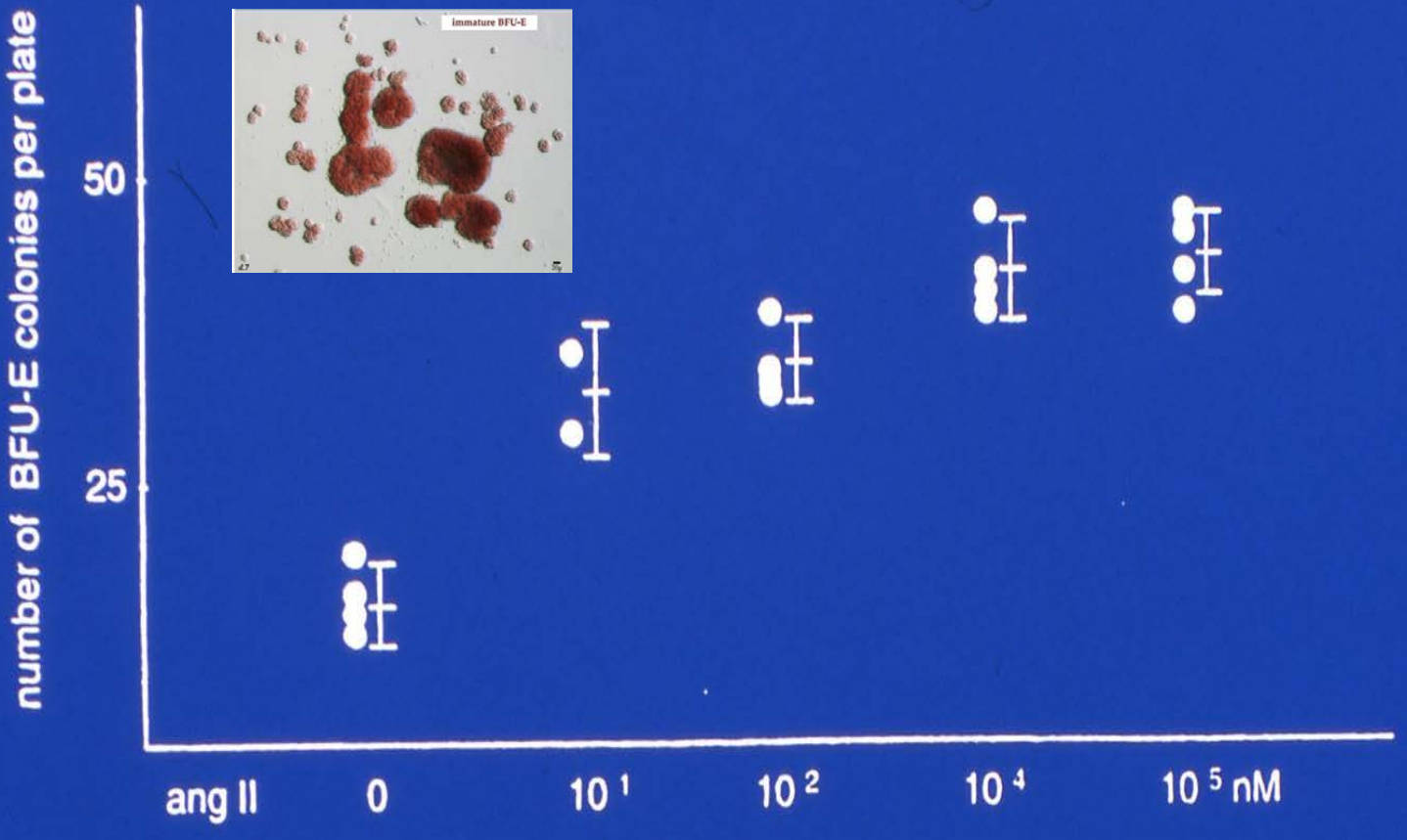


Figure 3. Angiotensin II (ang II) augments number of BFU-Es. Preincubation of early hematopoietic progenitors with angiotensin II–augmented proliferation of early erythroid precursors in the presence of maximal stimulatory concentration of erythropoietin (3 IU/ml).

MRUG ET AL, JCI, 1997

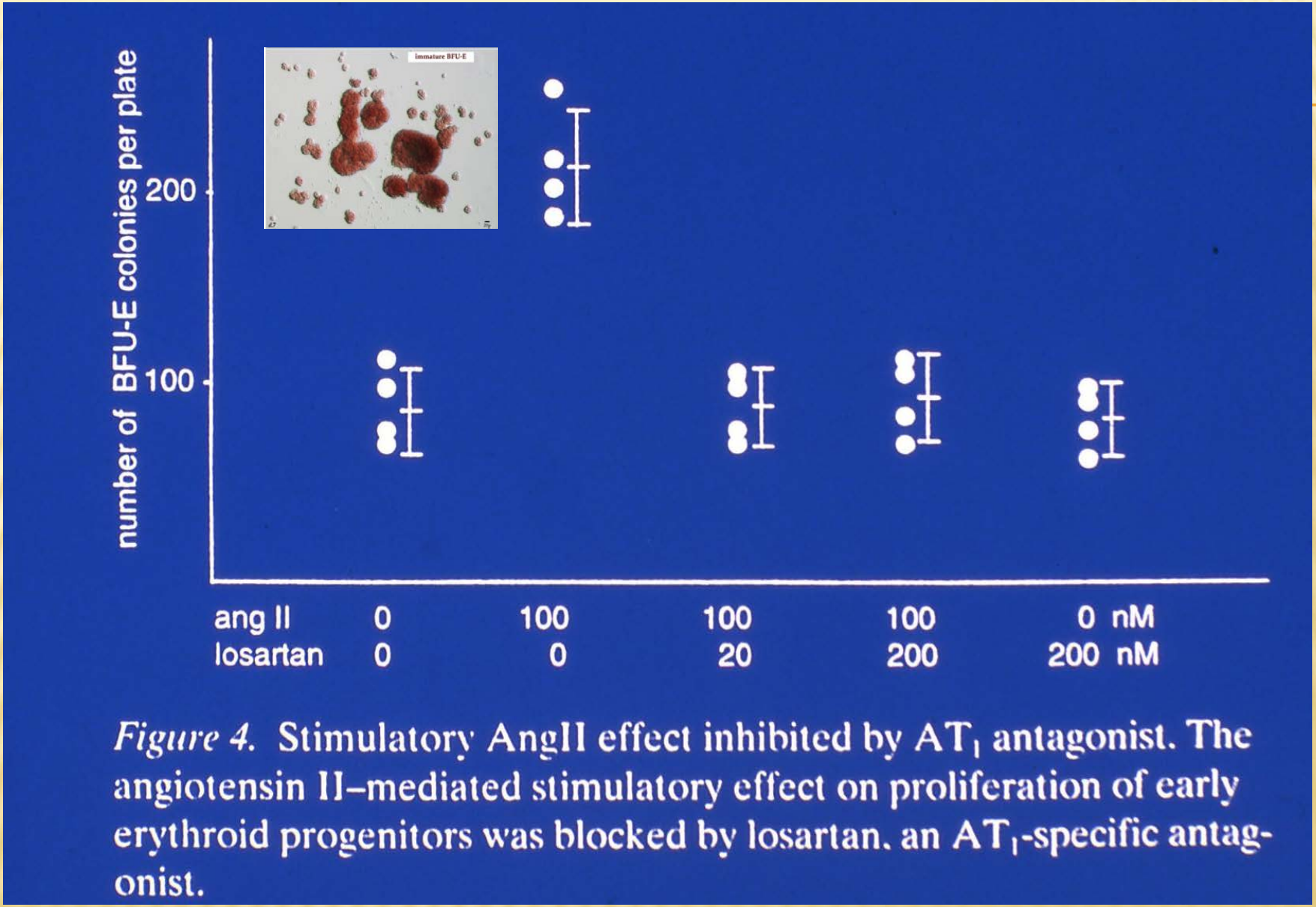
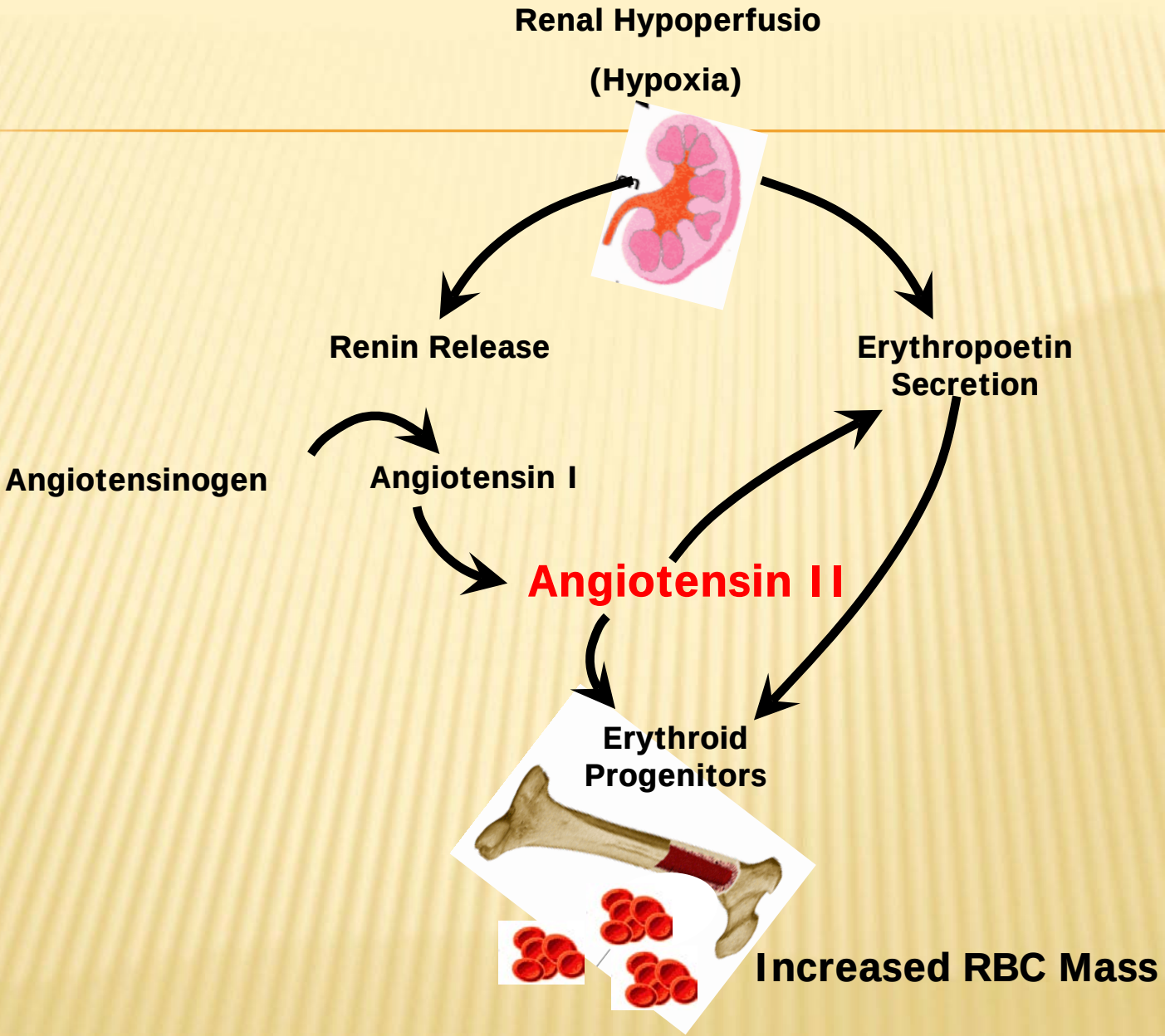


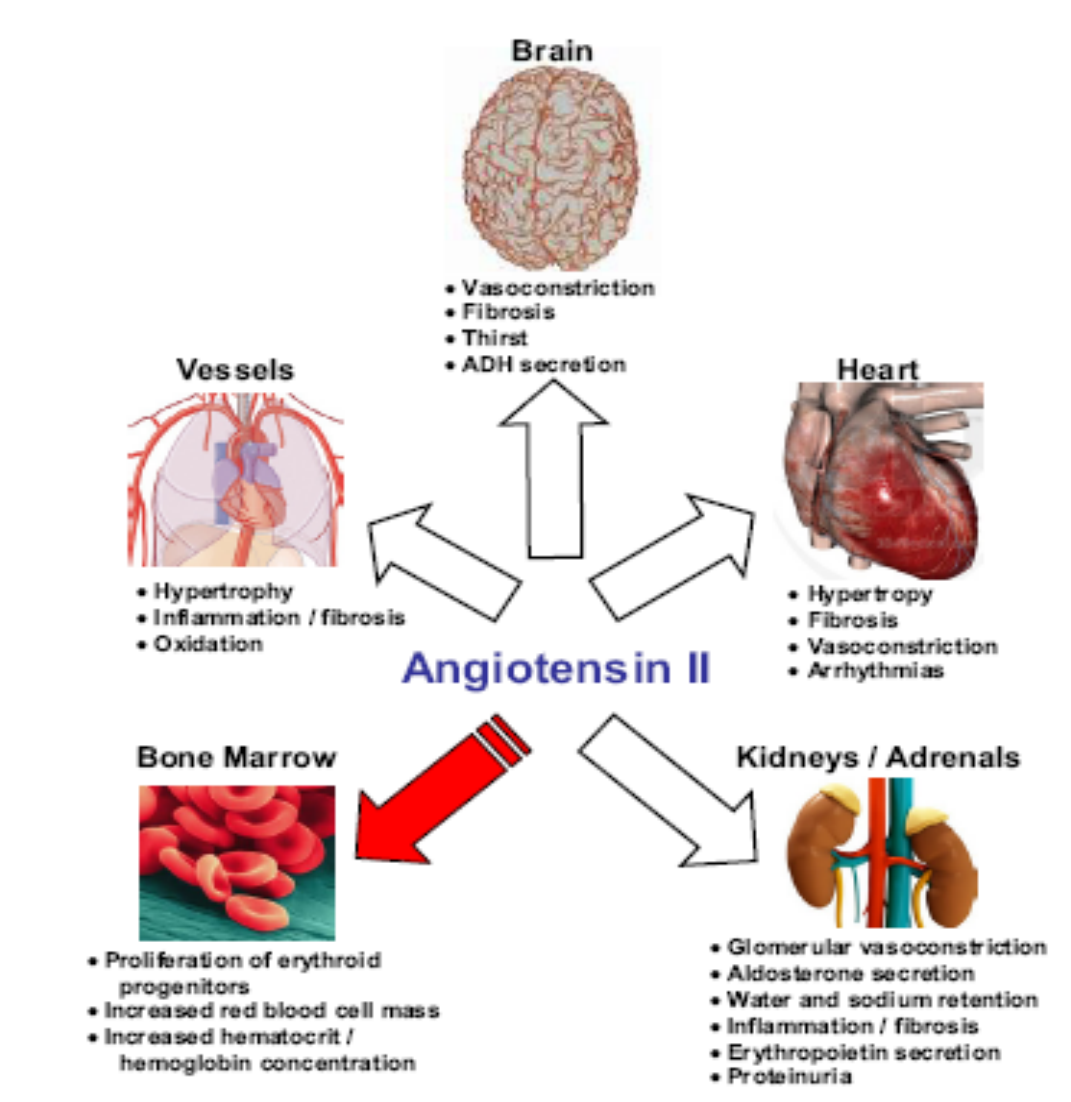
Figure 4. Stimulatory AngII effect inhibited by AT_1 antagonist. The angiotensin II–mediated stimulatory effect on proliferation of early erythroid progenitors was blocked by losartan, an AT_1-specific antagonist.

MRUG ET AL, JCI, 1997



Vlahakos, Marathias, Madias AJKD 2010

Vlahakos et al. AJKD 2010



ΣΥΜΠΕΡΑΣΜΑΤΑ

- Το ενεργοποιημένο ΣΡΑ και ειδικότερα η Αγγειοτασίνη ΙΙ αυξάνει την ερυθροποίηση και μέσω αύξησης της έκκρισης της ερυθροποιητίνης και ως αυξητικός παράγων στις άωρες μορφές των ερυθρών αιμοσφαιρίων μέσω υποδοχέων ΑΤ1.

- Η απενεργοποίηση του με αΜΕΑ ή σαρτάνη μπορεί να προκαλέσει δοσο-εξαρτώμενη μείωση του αιματοκρίτη ή/και αναιμία, που φθάνει στο ναδίρ εντός τριμήνου και είναι αντιστρεπτή με την διακοπή του φαρμάκου.

- Η αναστολή του ΣΡΑ μπορεί να χρησιμοποιηθεί για διόρθωση της πολυερυθραιμίας μετά την μεταμόσχευση νεφρού, σε ασθενείς με ΧΑΠ και σε διαβιούντες σε μεγάλα υψόμετρα.


Ευχαριστώ για την προσοχή σας!