The Kidney in Hypertension

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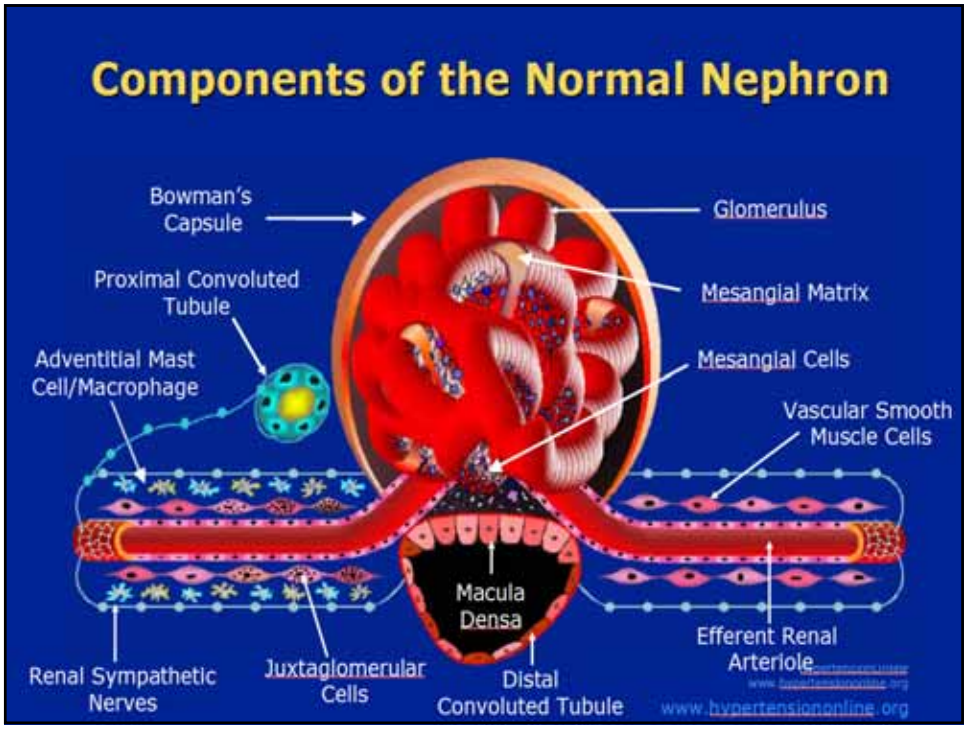
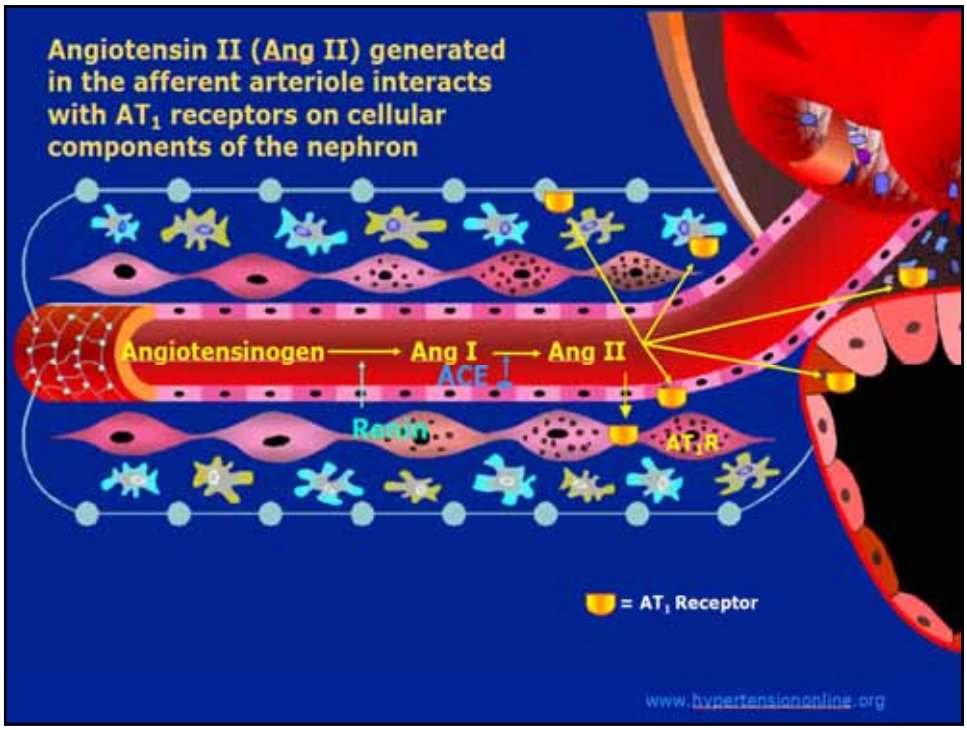
Outline

- Pathophysiology of hypertension in chronic kidney disease (CKD)
  - Renin-Angiotensin-Aldosterone System
- Case Study #1
  - Hypertension in Proteinuric Hypertensive Nephrosclerosis
- Case Study #2
  - Hypertension in Chronic Kidney Disease and Fluid Overload
- Case Study #3
  - Hypertension in Diabetic Nephropathy
- New potential therapies on the horizon

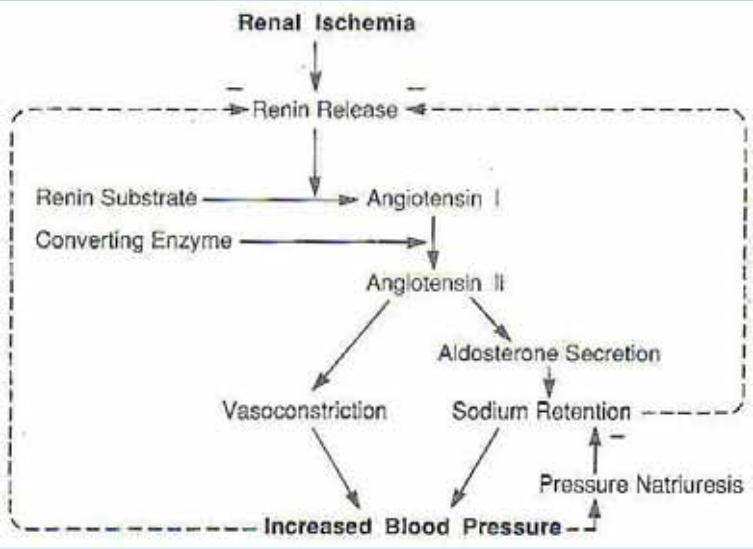

Components of the Normal Nephron
Bowman's Capsule
Glomerulus
Proximal Convoluted Tubule
Mesangial Matrix
Adventitial Mast Cell/Macrophage
Mesangial Cells
Vascular Smooth Muscle Cells
Macula Densa
Efferent Renal Arteriole
Renal Sympathetic Nerves
Juxtaglomerular Cells
Distal Convoluted Tubule
www.hypertensiononline.org


Angiotensin II (Ang II) generated in the afferent arteriole interacts with AT1 receptors on cellular components of the nephron
Angiotensinogen
Ang I
Ang II
ACE
Renin
AT1R
= AT1 Receptor
www.hypertensiononline.org

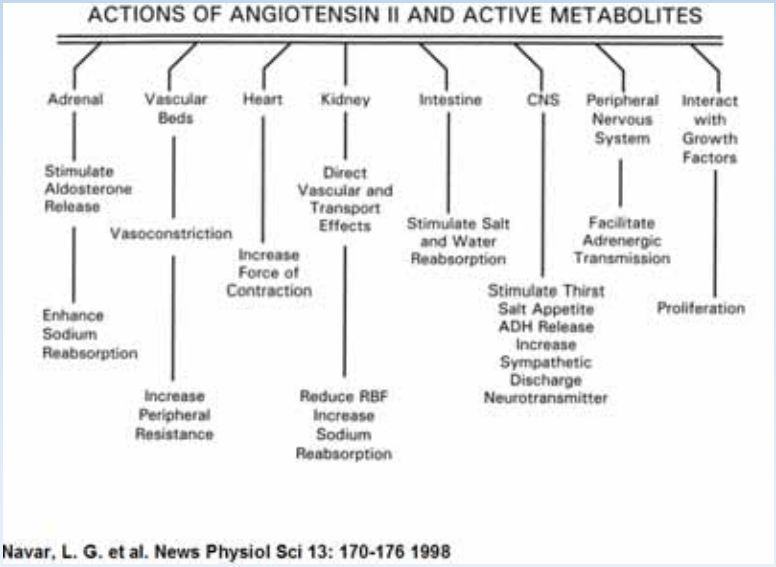
Stimuli to Increase Renin Production

- Mechanical
  - Decrease stretch/low blood pressure
- Chemical
  - Decrease sodium delivery to macula densa
- Neuronal
  - Increase in sympathetic tone

Renin-Angiotensin-Aldosterone System

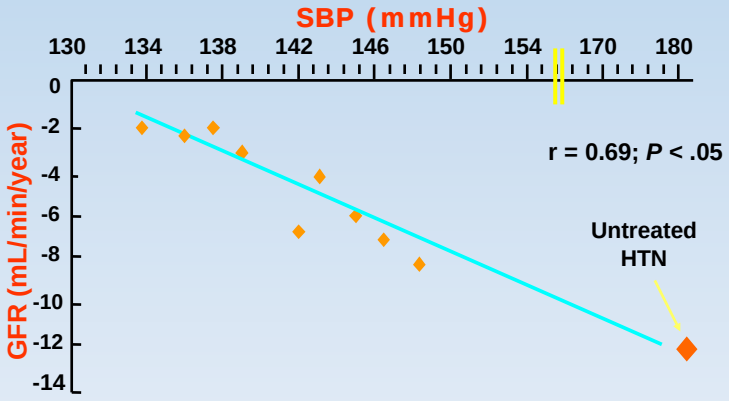


Angiotensin II



Navar, L. G. et al. News Physiol Sci 13: 170-176 1998

Meta Analysis: Lower Systolic BP Results in Slower Rates of Decline in GFR in Diabetics and Non-Diabetics



Parving HH, et al. Br Med J. 1989.
1996.
Viberti GC, et al. JAMA. 1993.
Klahr S, et al. N Eng J Med. 1994.
Hebert L, et al. Kidney Int. 1994.
Lebovitz H, et al. Kidney Int. 1994.
Moschio G, et al. N Engl J Med.
Bakris GL, et al. Kidney Int. 1996.
Bakris GL. Hypertension. 1997.
The GISEN Group. Lancet. 1997.

Bakris GL, et al. Am J Kidney Dis. 2000;36(3):646-661.

www.hypertensiononline.org

Case Study #1

- 63 yo woman with hypertension and hypertensive nephrosclerosis presents for follow up
- Medications:
  - Lisinopril 20mg qd
  - Amlodipine 5mg qd
- VS: 154/84, 74

Case Study #1

- Labs: Creat 1.3(baseline), normal electrolytes, spot urine protein/spot urine creatinine = 1.5g
- You increase lisinopril to 40mg qd and recheck basic metabolic panel in 1 week
- Creat now 1.6, normal electrolytes

Case Study #1:Question #1

- What do you do?
  - A. Stop lisinopril and instead increase amlodipine
  - B. Decrease lisinopril back to 20mg and increase amlodipine instead
  - C. Make no change in medications and repeat basic metabolic panel in 1 week
  - D. Panic

Answer

- C
- Make no change in medications and repeat basic metabolic panel in 1 week

Why Do We Tolerate an Increase in Creatinine?

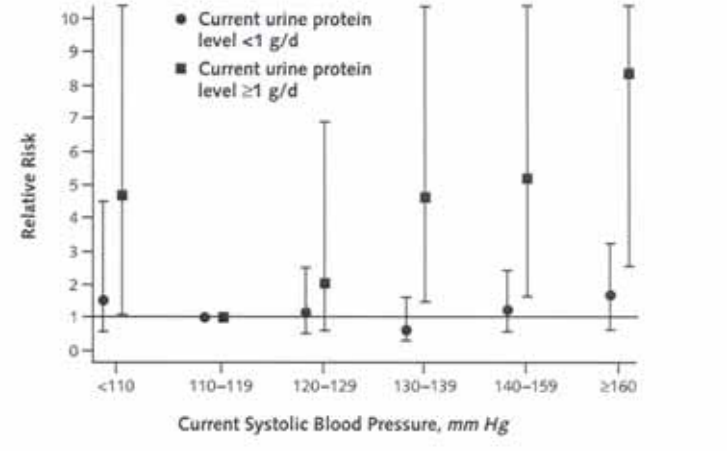
- Answer: There is an initial decrease in GFR which is reversible. Ultimately there is a slower decline in kidney function over time.

	Baseline	4 weeks	*P*
BP *(mm Hg)*[a]	140/82 (2/1)	151/89 (2/1)	< 0.0005
MAP *(mm Hg)*[a]	101 (1)	109 (1)	< 0.0001
GFR *(ml/min/1.73 m²)*[a]	76 (4)	81 (4)	< 0.0001
Albuminuria *(mg/24 hr)*[b]	704 (1.2)	1122 (1.2)	< 0.0001

[a] Mean (SEM)
[b] Geometric mean (antilog SEM)

Hansen et al. *Kidney Int* 1995;47:1726-1731.

Importance of Proteinuria in CKD Progression



Jafar, TH, et al. *Ann Internal Medicine*. 2003;139:244-252.

Case Study #2

- 77 yo man with hypertenisive nephrosclerosis, CHF, chronic LE edema with recurrent cellulitis presents for routine follow-up
- Medications
  - Aspirin
  - Coreg 80mg qd
  - Benazepril 40mg bid
  - Furosemide 60mg qd

Case Study #2

- PE
  - 179/83, 56, 317 lbs (nl 300 lbs)
  - Neck – elevated JVP
  - Lung – clear
  - CV – RRR
  - Ext – marked edema
- Labs
  - Creat 1.6 (baseline 1.9), nl electrolytes, Hgb 9.6 (baseline 11.2)

Case Study #2:Question #1

- His creatinine is better (1.6 vs 1.9). Is his kidney function
  - A. Better
  - B. Worse
  - C. The Same
  - D. Can't tell

ANSWER

- D
- Can't tell

Creatinine Is a Concentration

- Our patient has a decrease in serum creatinine in setting of severe fluid overload
- The creatinine can be falsely lower in this situation secondary to a dilutional effect

Case Study #2

- Patient advised to increase furosemide to 100mg a day and recheck basic metabolic panel in a week.
- Repeat lab shows creatinine up to 2.3 from 1.6

Case Study #2:Question #2

What do you do?

A. Advise patient to stop diuretic and repeat lab in a week

B. Advise patient to stop diuretic and ace-inhibitor and repeat lab in 1 week

C. Advise patient to continue current medications and repeat lab in 1 week

D. Panic

ANSWER

- C
- Advise patient to continue current medications and repeat lab in 1 week

Importance of fluid control

- Cardiac function
- Blood pressure management
- Decrease risk of recurrent cellulitis
- Patient comfort/mobility

- Treat the patient, not the number (creatinine)

Case Study #2

- Patient returns after 1 month

- PE
- 114/65, weight 305lbs
- Improved LE edema

- Hgb up to 10.7, creatinine steady at 2.3

Case Study #2: Question #1 - Revisited

- His creatinine is better (1.6 vs 1.9). *This is in a setting of fluid overload.* Is his kidney function
  - A. Better
  - B. Worse
  - C. The Same
  - D. Can't tell
- Answer – B. worse – new creatinine is 2.3

Case Study #3

- 67 yo woman with poorly controlled diabetes, diabetic retinopathy, diabetic nephropathy presents for routine follow up
- Medications
  - Lisinopril 20mg qd
  - Insulin
  - Amlodipine 5mg qd
  - Simvastatin 10mg

Case Study #3

- PE
- 165/95, 71, BMI 36
- Ext – trace edema

- Labs
- Creat 1.2, K 5.5, albuminuria 3500mg

Case Study #3: Question #1

How do you treat her HTN?

A. Advise her to exercise, watch sodium, and lose weight

B. Increase lisinopril, add thiazide diuretic, and check basic metabolic panel in 1 week

C. Stop Ace-inhibitor and increase amlodipine/start another agent

D. A&B

E. A&C

ANSWER

- D

- Advise her to exercise,watch sodium and lose weight
- Increase lisinopril, start thiazide diuretic and check basic metabolic panel in 1 week

Lifestyle Modifications - JNC7

Modification	Approximate SBP Reduction (range)
Weight Reduction	5-10 mmHg/10kg
Dietary sodium reduction	2-8 mmHg
Physical activity	4-9 mmHg
Moderation of alcohol consumption	2–4 mmHg

JNC 7. *JAMA*. 2003;289:2560-2572.

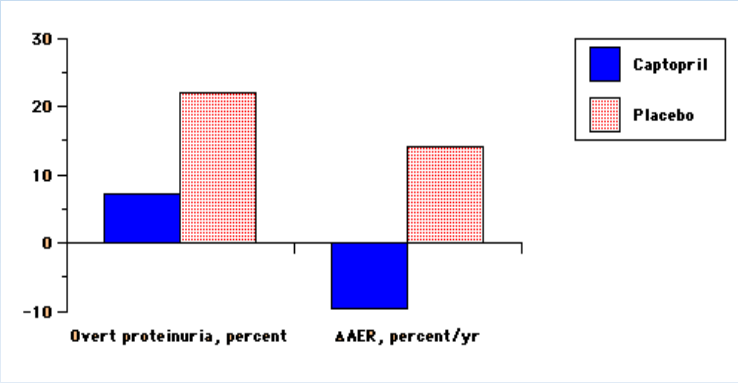
Issues

Decrease Progression of Diabetic Nephropathy

- Control Hypertension
- Decrease Proteinuria (RAAS blockers)

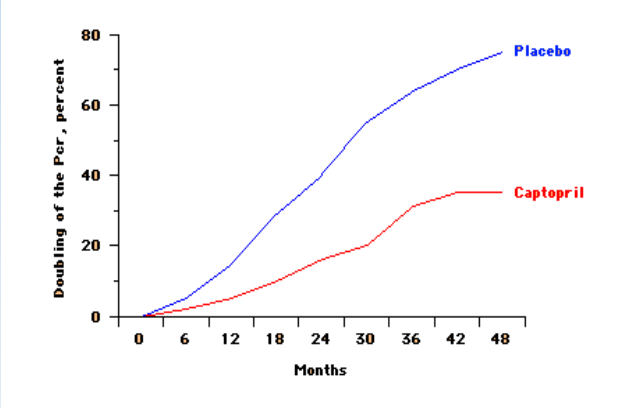
Control of Potassium

ACE Inhibitors Lessen Chance of Progression to Overt Nephropathy



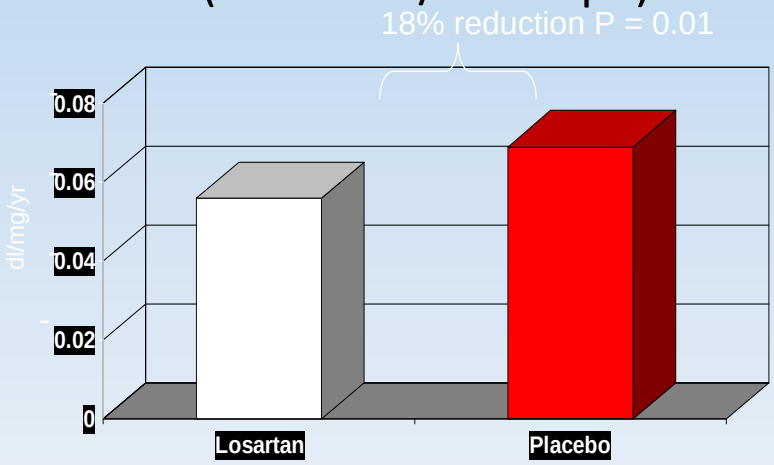
Diabetologia 1996;39: 587

Captopril Retards Progression of Diabetic Nephropathy in Type I Diabetes



NEJM 1993;329:148

RENAAL: Rate of Progression of Renal Disease (median 1/sCr slope)



Brenner BM et al NEJM 2001;345:861-869.

Hyperkalemia in Diabetes

- Type 4 renal tubular acidosis (hyporeninemic hypoalderstonism)
- Medications induce hyperkalemia – all RAAS blockers (Ace-Inhibitors, ARBs, Renin-inhibitors, aldosterone antagonists)

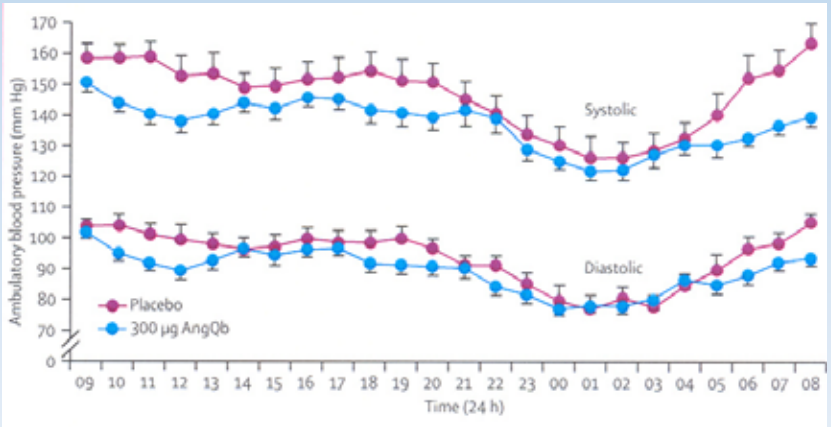
Control of Hyperkalemia

- Need to monitor patients
- Dietary potassium restriction (less than 2000-3000mg/day)
- Use of diuretics (thiazides and loop diuretics)

Potential Treatments on the Horizon

- Hypertension Vaccine
- Renal Denervation
- Vasopeptidase Inhibitors

Vaccine Against Angiotensin II



Tissot AC el al. *Lancet* 2008;371:821-27.

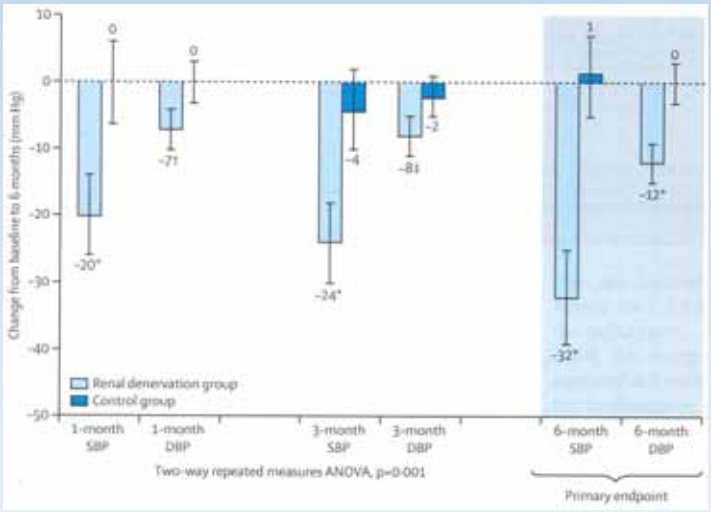
Hypertension Vaccine

	100 µg		300 µg	
	Placebo (n=12)	AngQb (n=22)	Placebo (n=12)	AngQb (n=21)
Systolic blood pressure day	-3·4 (2·3)	-1·5 (1·7)	3·4 (2·8)	-5·5 (2·1)*
Diastolic blood pressure day	-1·6 (1·8)	0·0 (1·3)	1·1 (1·7)	-2·9 (1·2)†
Systolic blood pressure night	-2·6 (3·2)	1·1 (2·3)	-2·5 (4·0)	-1·2 (3·0)
Diastolic blood pressure night	1·7 (2·0)	1·3 (1·5)	-1·8 (2·3)	-0·8 (1·7)

Data are mean (SE). *p=0·012 compared with baseline. †p=0·024 compared with baseline.

Table 5: **Change from baseline in ambulatory blood pressure for treatment groups**

Renal Denervation
Symplicity HTN-2 Trial

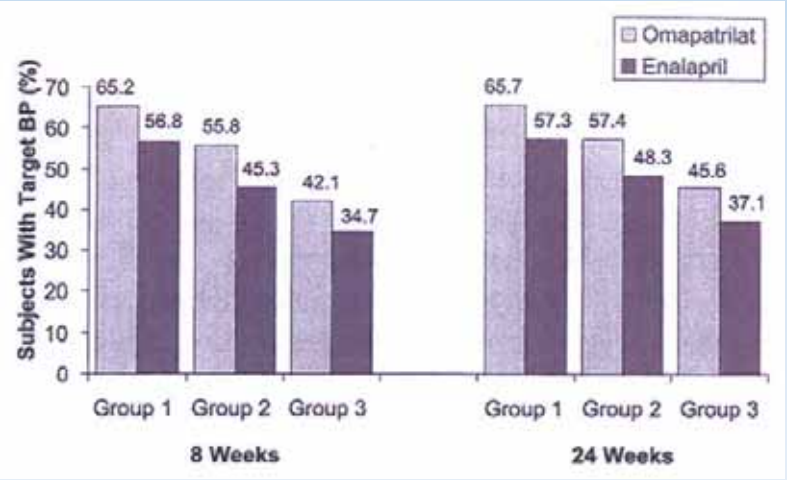


Lancet 2010;376:1903-09.

Vasopeptidase Inhibitors

- Inhibit angiotensin coverting enzyme
- Inhibit neutral endopeptidase
  - Prolongs activation of natriuretic peptides

OCTAVE Trial



Kostis JB et al. *Am J Hypertens* 2004;17:103-111.

Summary

- Kidney disease and hypertension go hand in hand
- Importance of blood pressure control (<130/80)
- Importance of decreasing proteinuria
- Watch for hyperkalemia