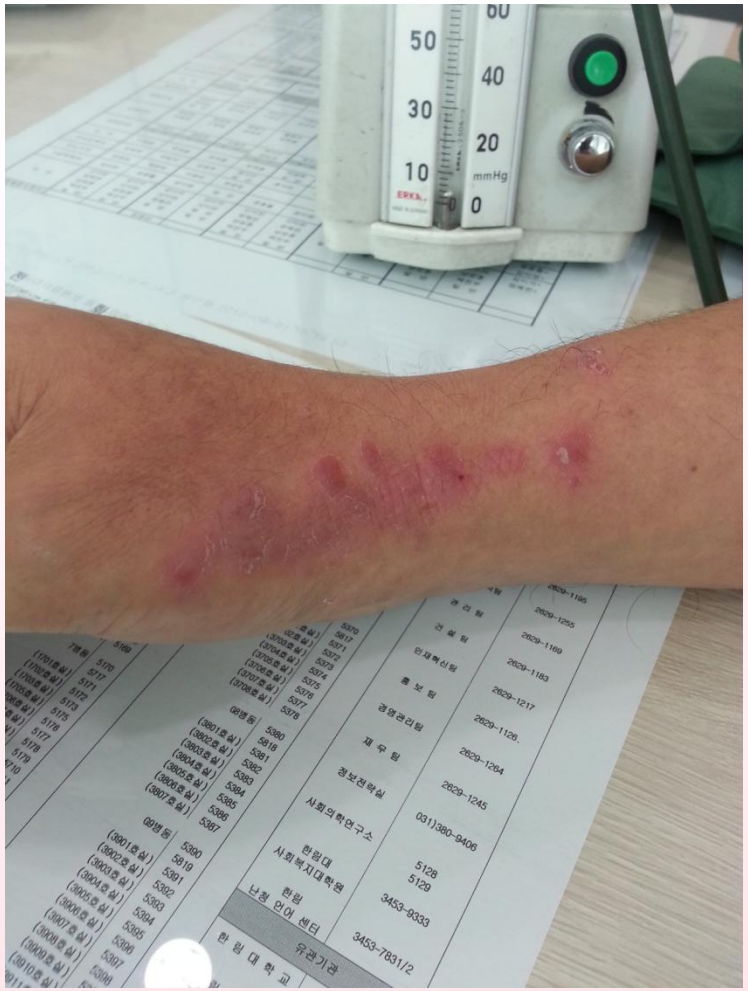
Drug induced hypertension

Hallym University Medical Center

Seong Woo Han

- 47-yrs male
- BP 180/100mmHg

- Dermatitis for 1 mo
- PD 10mg
- Antihistamine



Secondary causes of HTN

- Renal
- Renovascular
- Adrenal
- Aortic coarctation
- Obstructive sleep apnea
- Neurogenic
- Miscellaneous endocrine
- Medications

Medications associated with HTN

- Adrenal steroid
- NSAIDs
- Sex hormone
- Anti-depressant
- Decongestant
- Cyclosporine
- VEGF inhibitor
- Erythropoietin
- Appetite suppressant

Mechanisms of drug induced HTN

- Volume retention
- Endothelial dysfunction
- Sympathetic n. system activation
- RAAS activation
- Combined mechanisms
- Unknown

Glucocorticoid

Glucocorticoid

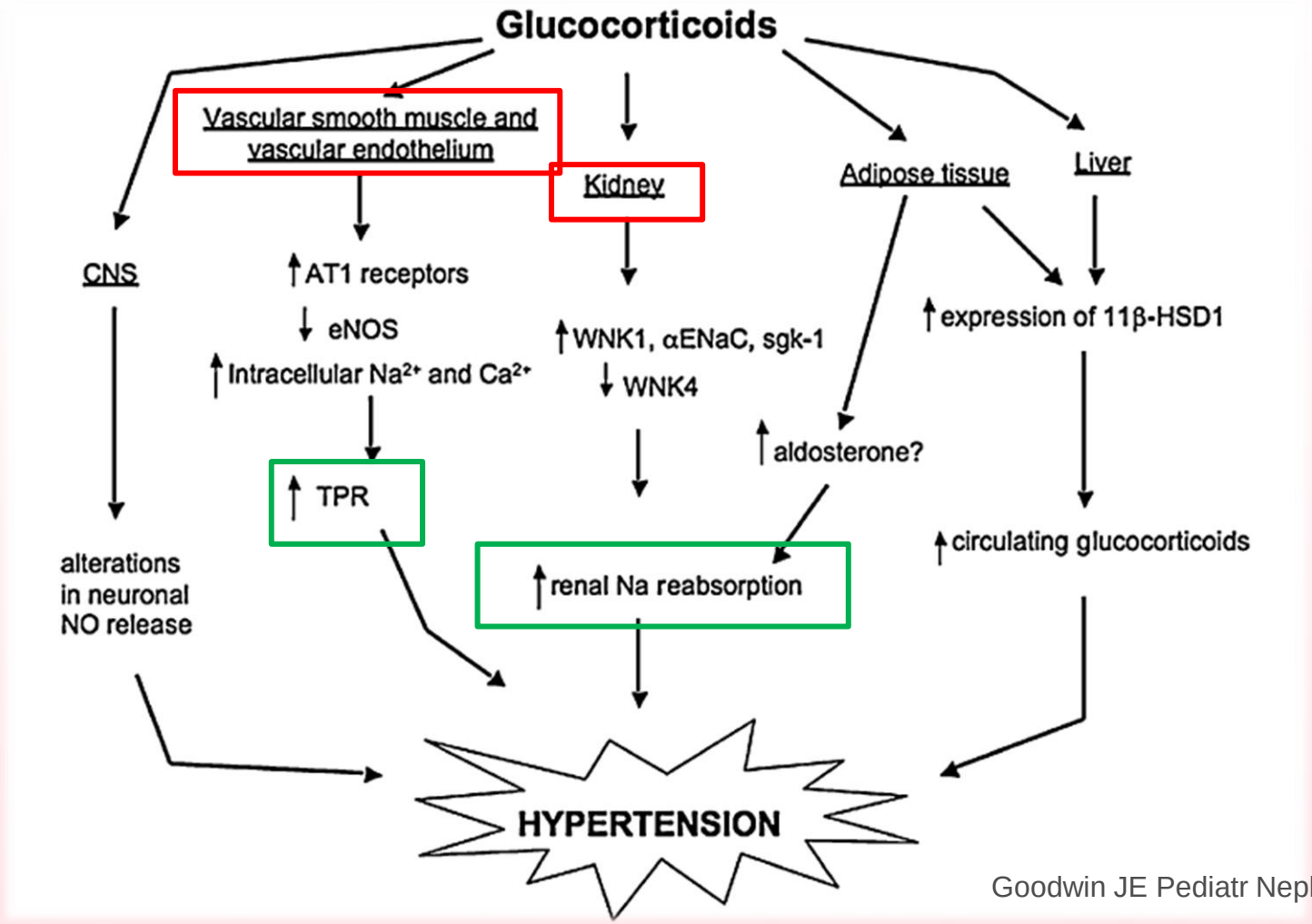
- Replacement therapy
- Rheumatologic disease
- Dermatologic disease
- Allergic state
- Ophthalmic disease
- Inflammatory bowel disease
- Hematologic & malignancy
- Nephropathy
- Pain clinic

Epidemiology: GC mediated HTN

- 70% of Cushing's syndrome has HTN
- CV mortality of Cushing's syndrome x4↑
- 20% of pts with high dose corticosteroid develop HT
- 80-200mg oral cortisol → SBP 15mmHg↑ within 24h

Mechanisms of GR induced HTN

- Renal
  - Mineralocorticoid receptor
  - Glucocorticoid receptor
  - → Renal Na^+ reabsorprtion ↑
- Vascular
  - Glucocorticoid receptor
  - Endothelium, SMC
  - → AT 1 receptor ↑
  - → Na^+, Ca^{++} influx ↑
  - → eNOS ↓, NO ↓



Goodwin JE Pediatr Nephrol 2012

Management of GC mediated HT

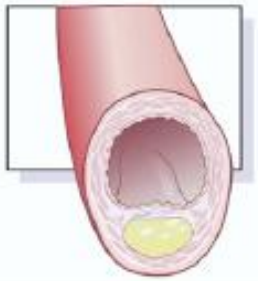
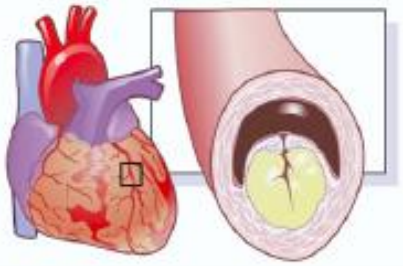
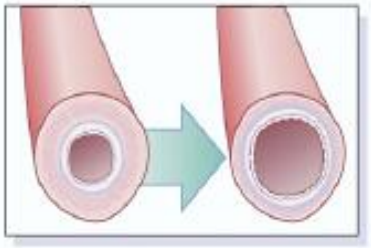
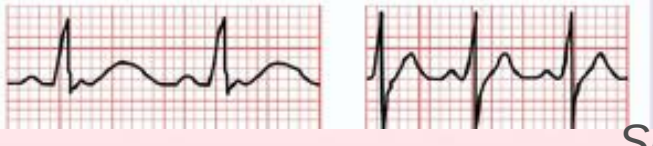
- Cessation of GC
- Diuretics are choice
- ACEi or ARB may be required
- Mandatory monitoring of K^+

Mineralocorticoid

Mineralocorticoid like action (high BP, low K^+)

- Licorice, ketoconazole : 11β-hydroxysteroid-dehydorg enase inhibition → mineralocorticoid excess state
- Skin ointment, hemorrhoid cream: : 9-α fluoro-prednisolone
- Ophthalmic solution: 9- α fluoroprednisolone

Oral contraceptive

Estrogens		Progestins
↓ LDL oxidation ↓ LDL binding ↑↓ lipoprotein* *** ↑ blood pressure ↓ oxidation damage ↓ VSMC proliferation ↓ glucose tolerance***	**Atherosclerosis** 	↑↓ HDL effect* ** ↑↓ blood pressure** ↑ glucose tolerance**
↑ coagulation factors ↓ platelet aggregation	**Thrombosis** 	↑ coagulation factors ↓ platelet aggregation ↓ nitric oxide**
↑ nitric oxide ↓ endothelin ↑ Cox-2 ↓ neuroendocrine response ↓ VSMC proliferation	**Vasomotion** 	↑ vasoconstriction** ↓ nitric oxide**
↑ QT prolongation	**Arrhythmogenesis** 	↓ QT prolongation

Shufelt JACC 2009

Risk for hypertension by OCs

"Nurse's Health Study II"
68,297 women, 4yrs, 231,006 person-yr

	OCs use		
	Never	Past	Current
Person-yr	35,333	167,236	28,437
Multivariated RR	1.0	1.2 (1.0-1.4)	1.8 (1.5-2.3)
Multivariated + BP adjusted RR	1.0	1.2 (1.1-1.5)	1.9 (1.6-2.4)

Chasan-Taber Circulation 1996

Risk by progestrone and estrogen potency

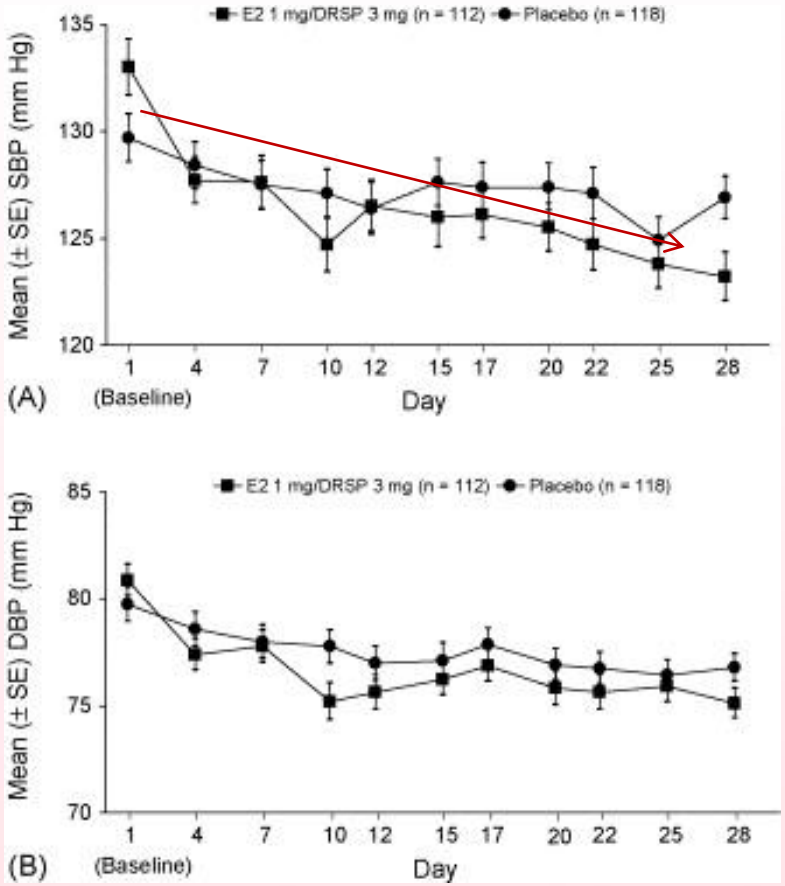
	RR	95% CI
Progesterone		
Never	1.0	Referent
Low (<1mg)	1.6	1.1-2.2
Medium (1mg)	2.5	1.9-3.4
High (> 1mg)	2.0	1.4-3.0
Estrogen		
Never	1.0	Referent
Low (≤30μg)	1.9	1.5-2.5
Medium (>30-≤50μg)	2.2	1.7-2.8
High (>50μg)	.	

Chasan-Taber Circulation 1996

Currently available OCs in Korea

Name	Estrogen	Progestin
Myvlar (마이보라)	EE 30μg	Gestodene 75μg
Meliane (멜리안)	EE 20μg	Gestodene 75μg
Minivlar (미니보라)	EE 30μg	Levonorgestrel 0.15mg
Yasmin (야스민)	EE 30μg	Drospirenone 3.0mg
Yaz (야즈)	EE 20μg	Drospirenone 3.0mg
Mecilone (머시론)	EE 20μg	Desogestrel 0.15mg

Drospirenone, anti-aldosterone effect

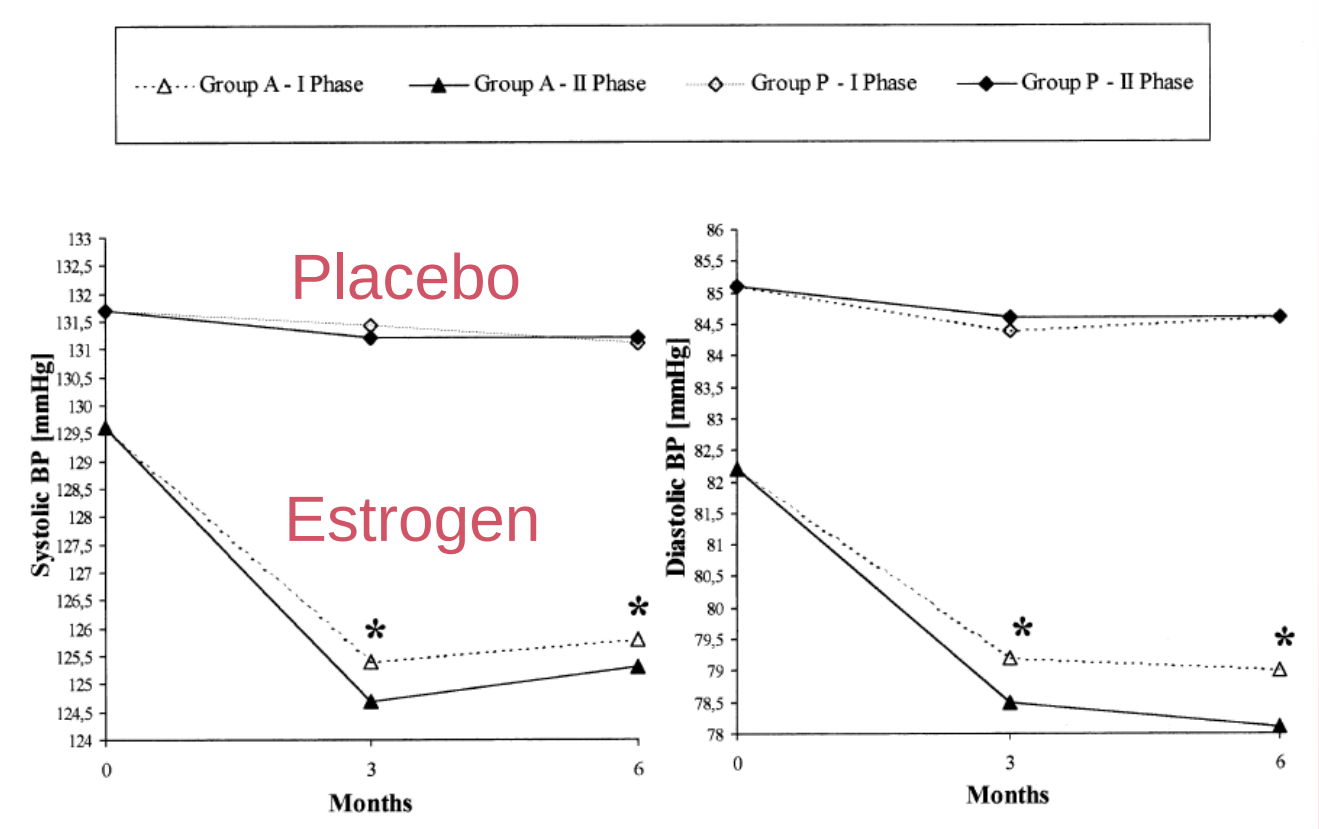


Palocious Maturitas 2006

Management of OCs associated hypertension

- Selection : well controlled BP, < 35yrs, healthy, non-smoking
- Monitor BP, if well controlled, continue
- If BP not controlled, progesterone only pills or IUD
- 4^{th} generation oral pills?

ERT on BP of hypertensive women



Affinito Maturitas 2001

NSAIDs and Coxib in HTN

Frequency of analgesic use and risk of HTN (Women)

"Nurse's Health Study"
121,700 women, 8yrs, 381078 person-yr

Frequency (d/wk)	0	1	2-3	4-5	6-7	p trend
Acetaminophen	1	1.08 (1.03-1.15)	1.13 (1.05-1.22)	1.38 (1.24-1.53)	1.21 (1.13-1.30)	<0.001
NSAIDs	1	1.07 (1.02-1.13)	1.22 (1.14-1.32)	1.31 (1.16-1.48)	1.20 (1.08-1.33)	<0.001
Aspirin	1	1.05 (0.99-1.12)	1.21 (1.12-1.31)	1.32 (1.12-1.48)	1.35 (1.25-1.46)	<0.001

Dedier . Hypertens 2002

Frequency of analgesic use and risk of HTN (Men)

"Health professional follow up study"
16,031 men, 4 years 52,673 person-yr

Frequency (d/wk)	0	1	2-3	4-5	6-7	p value
Acetaminophen	1	1.0 (0.74-1.35)	1.0 (0.78-1.29)	1.59 (1.13-2.24)	1.34 (1.00-1.79)	.01
NSAIDs	1	0.95 (0.77-1.18)	1.09 (0.92-1.29)	1.15 (0.85-1.54)	1.38 (1.09-1.75)	0.002
Aspirin	1	0.92 (0.69-1.22)	1.36 (1.14-1.61)	1.29 (1.05-1.57)	1.26 (1.14-1.40)	<0.001

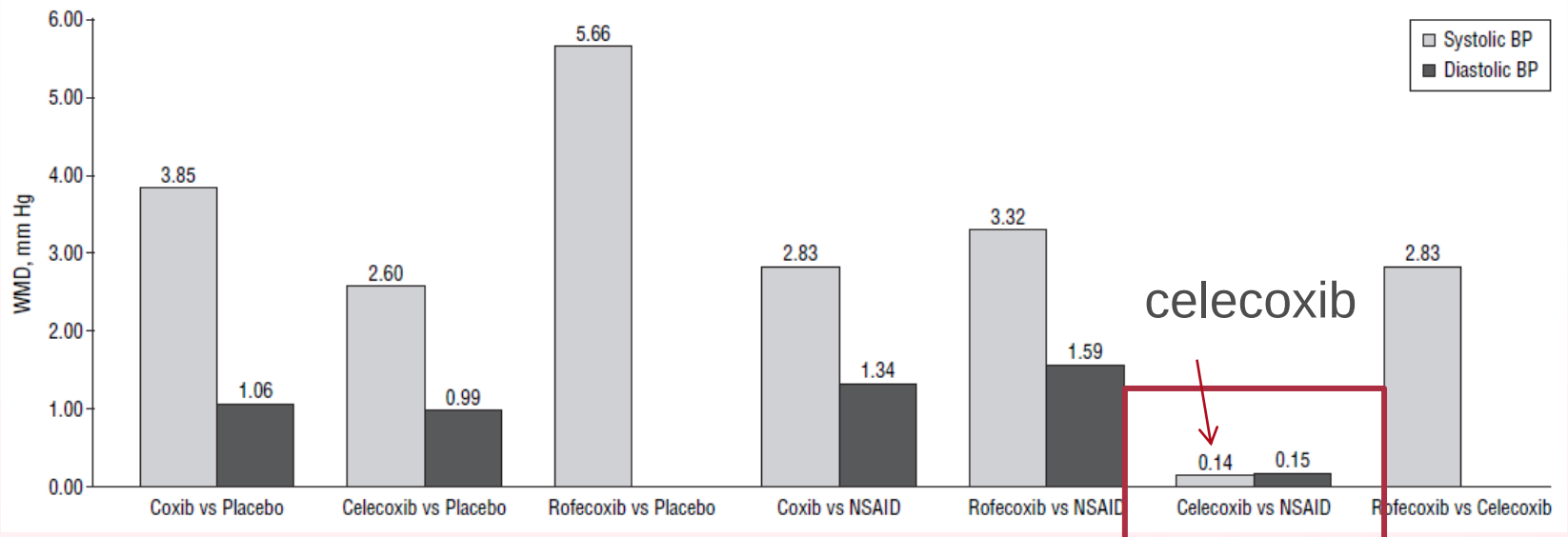
Forman Arch Int Med 2007

Change of BP in hypertensives and normotensives

	Hypertensive patients (mmHg)	Normotensive individuals (mmHg)
NSAIDs (pooled)	3.6–5.4	1.0–1.1
Indomethacin	4.8–6.0	1.0
Naproxen	3.1–6.1	ND
Piroxicam	2.9–6.2	ND
Sulindac	−1.6 to 2.2	−1.6
Aspirin	−1.8 to 1.0	0.6
COXIBs		
Rofecoxib	2.6–4.7	3.4
Celecoxib	−0.4	4.3

Armstrong Clin Ther 2003

COX -2 inhibitors on BP



Coxib vs placebo

Coxib vs placebo

Rofecoxib vs placebo

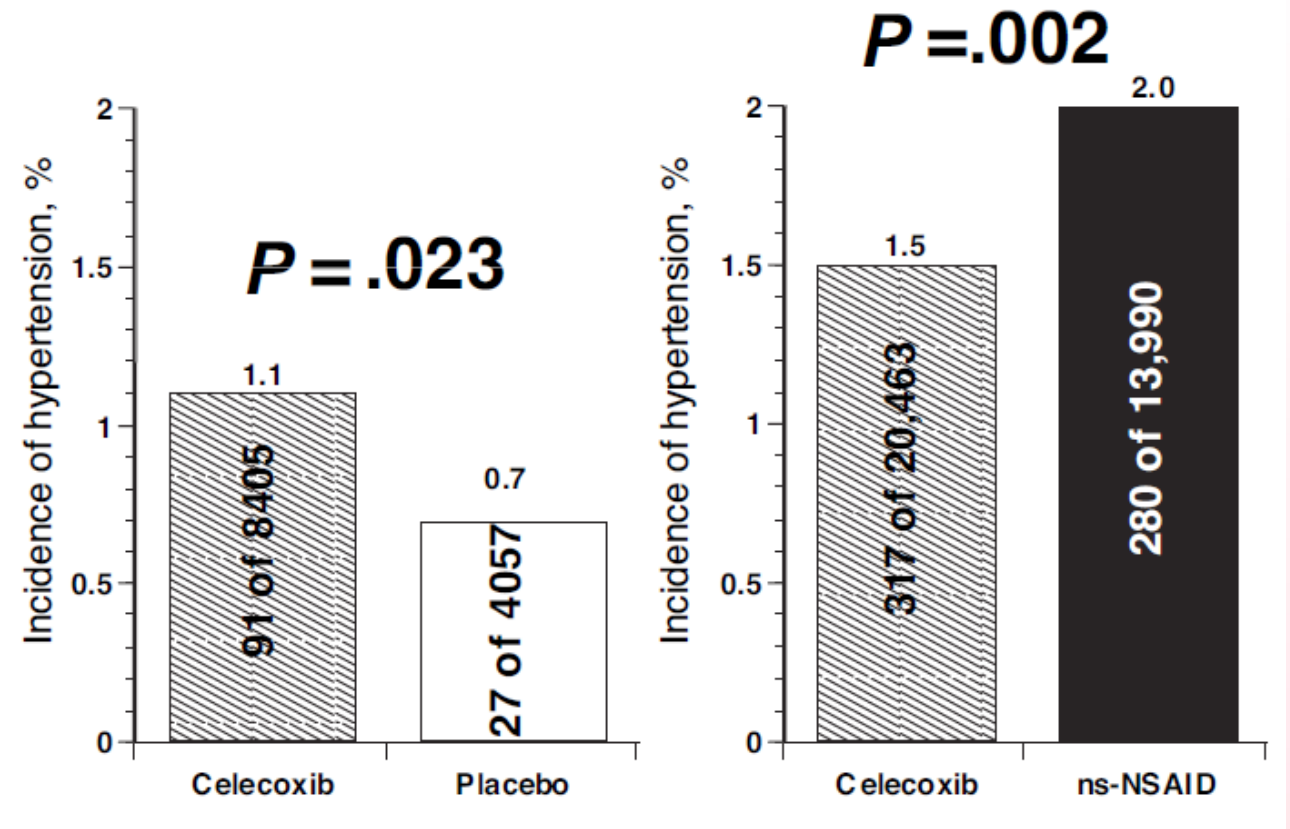
Coxib vs NSAIDs

Rofecoxib vs NSAIDs

Coxib vs NSAIDs

Tai-Juan. Arch Int Med 2005

Incidence of HTN Coxib vs NSAIDs



Elliott J Clin Hypertens 2006

High dose celecoxib also hazardous

celecoxib for prevention of colorectal Ca.

	APC		
	Placebo (n=678)	200 mg BID (n=683)	400 mg BID (n=665)
BP			
Baseline, mm Hg	131.7 ±17.2/80.0±9.6	131.6 ±15.9/79.2±8.8	130.5 ±15.9/78.7±9.4
1 y, mm Hg (n)	132.2 ±17.4/78.8±10.5 (603)	134.5 ±18.0/79.3±10.3 (608)	133.7 ±17.7/78.8±9.5 (598)
3 y, mm Hg (n)	130.7 ±17.2/77.3±10.1 (506)	133.0 ±17.0/78.2±9.9 (518)	134.2 ±18.5/77.9±9.8 (516)
Change in BP[1] from baseline compared to change in placebo,* mm Hg (95% CI)			
At 1 y	...	2.0 (0.1–4.0)/1.2 (−0.1–2.4)	2.9 (0.9–4.9)/1.2 (−0.1–2.4)
At 3 y	...	2.6 (0.2–4.9)/1.8 (0.4–3.3)	5.2 (2.9–7.6)/2.1 (0.6–3.5)
Patients with change in systolic BP on follow-up,† %			
At 1 y			
≥10 mm Hg	26±1.8	31±1.9	32±1.9
≥15 mm Hg	18±1.5	22±1.7	23±1.7
At 3 y			
10 mm Hg	24±1.9	31±2.0	36±2.1
≥15 mm Hg	16±1.6	21±1.8	27±2.0

Solomon. Circulation 2006

Mechanism, NSAIDs induced HTN

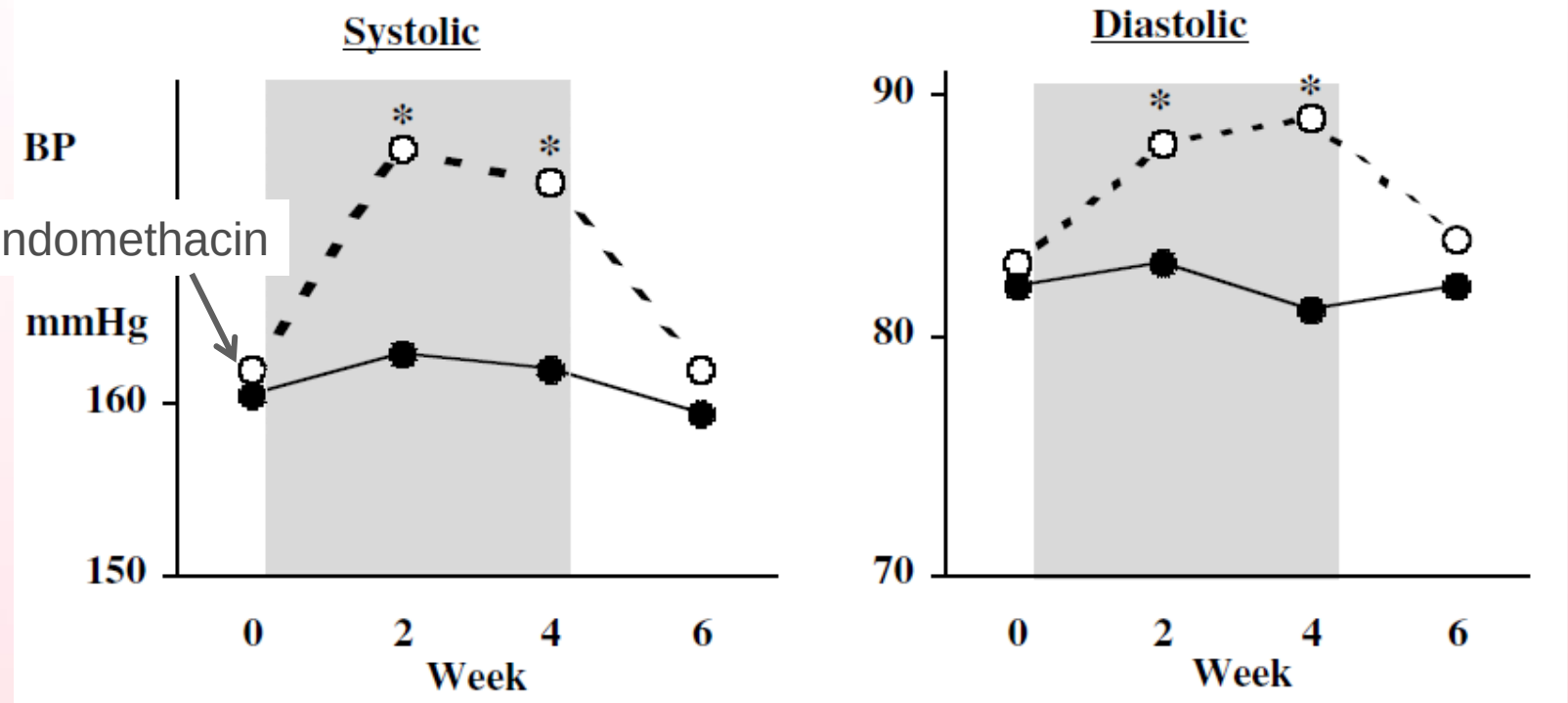
- Vasodilatory prostaglandin ↓
- Endothelial function ↓
- Renal Na^+ reabsorption ↑ (NSAIDs)
- Cellular oxidative stress ↑ (acetaminophen)

Risk factors for severe hypertension with NSAIDs

- Elderly patients
- Pre-existing hypertension
- Salt-sensitive patients
- Renal failure
- Renovascular hypertension

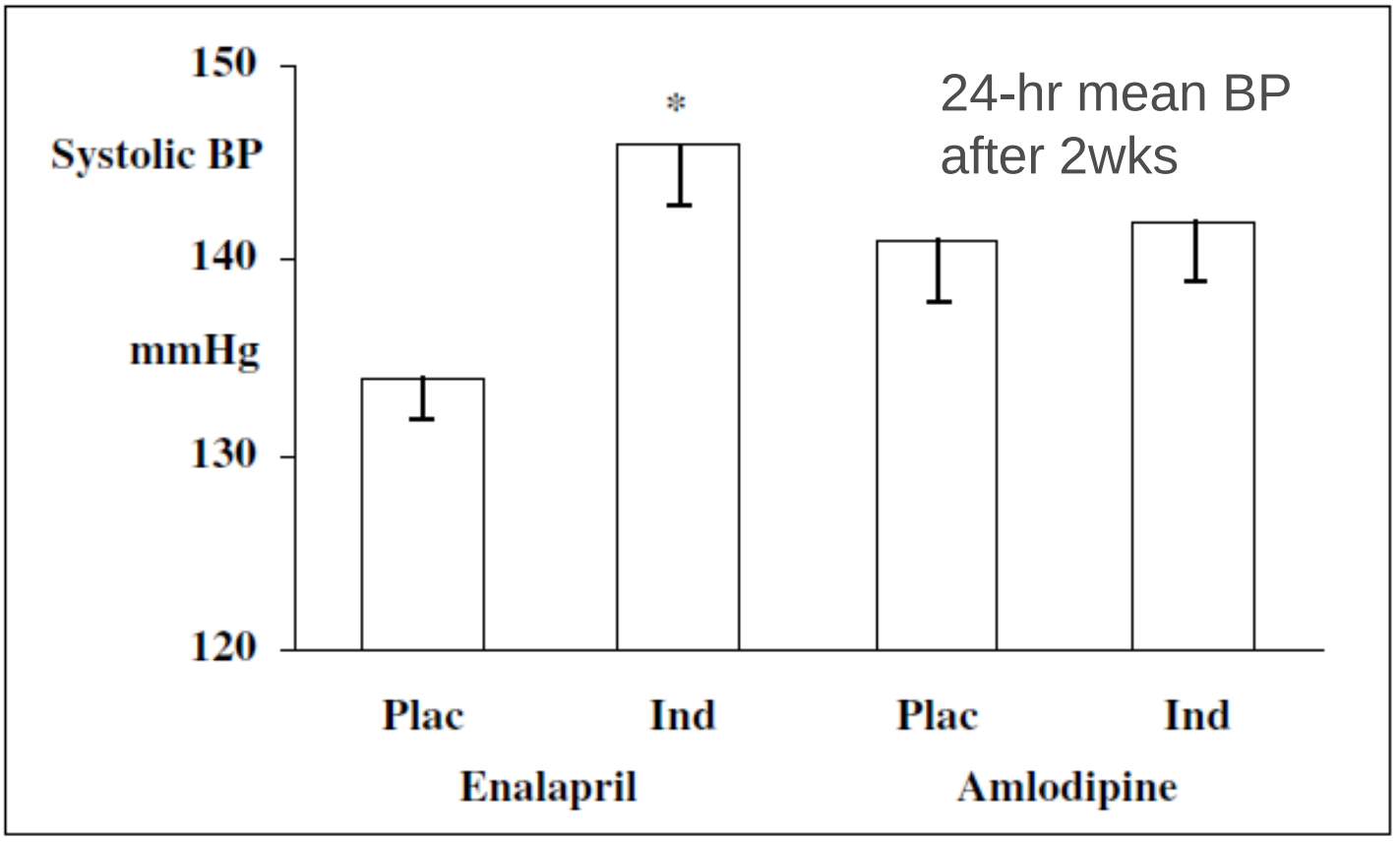
Different effect with different anti-HTN Rx

- Enalapril (n=15)
- Felodipine (n=12)



Morgan J Clin Hypertens 2002

Different effect with different anti-HTN Rx

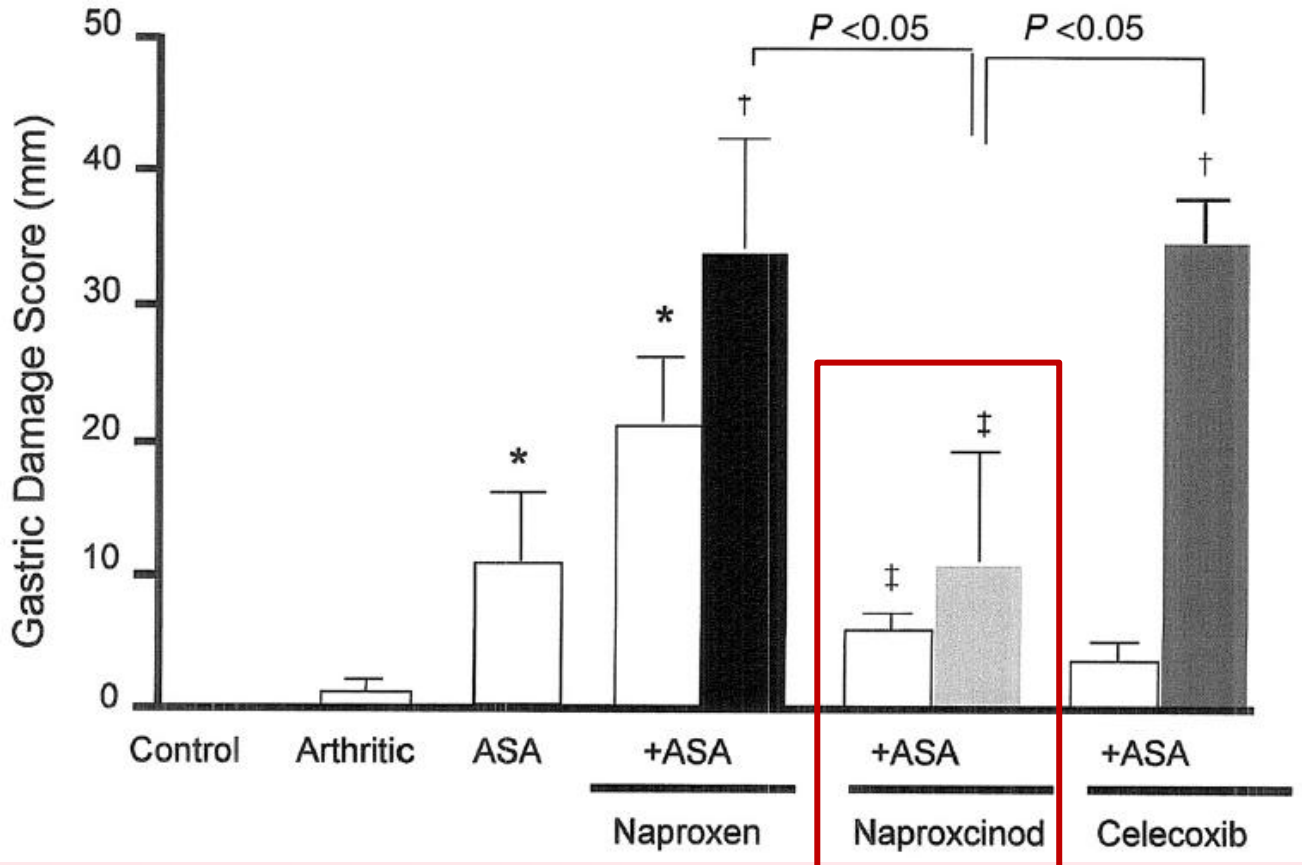


Morgan J Clin Hypertens 2002

NSAIDs or Coxib in HTN

- Potent BP elevation: indomethacin, naproxen, piroxicam, rofecoxib
- Antagonizing the effect of ACEi or ARB (lesser degree), beta-blockers
- CCB appear to be least influenced

Naproxen with NO donor



Fiorruci J Pharmacol Exp Ther 209

VEGF inhibitor (angiogenic inhibitor)

VEGF inhibitor

bevacizumab
Avastin®

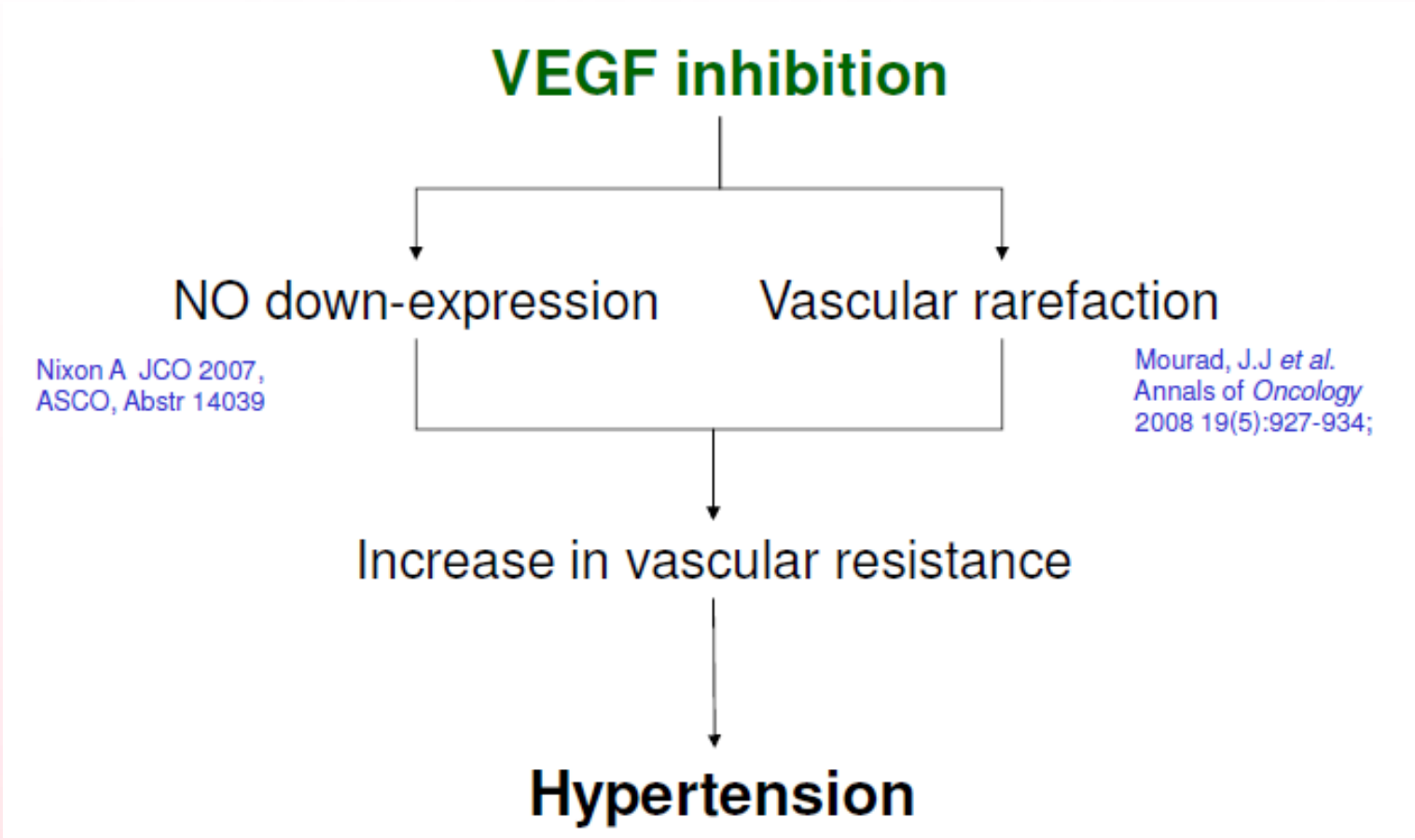
sunitinib
Sutent®

Sorafenib
Nexavar®

Relative risk of HT in VEGF trial

	Hypertension incidence [IC, 95%]	Relative risk [IC, 95%]
Bevacizumab (≥10mg/kg)	**25.4%** (21.3 - 30.1%)	**7.5** (4.2 - 13.4)
Sunitinib	**22.5%** (19.5 - 25.9%)	**3.9** (2.6 - 5.9)
Sorafenib	**23.4%** (16.0 - 32.9%)	**6.1** (2.4 - 15.3)
Axitinib	**61.0%**	**Unknown**
VEGF Trap	**31.6%**	**Unknown**

Mechanism of VEGF inhibitor induced HTN

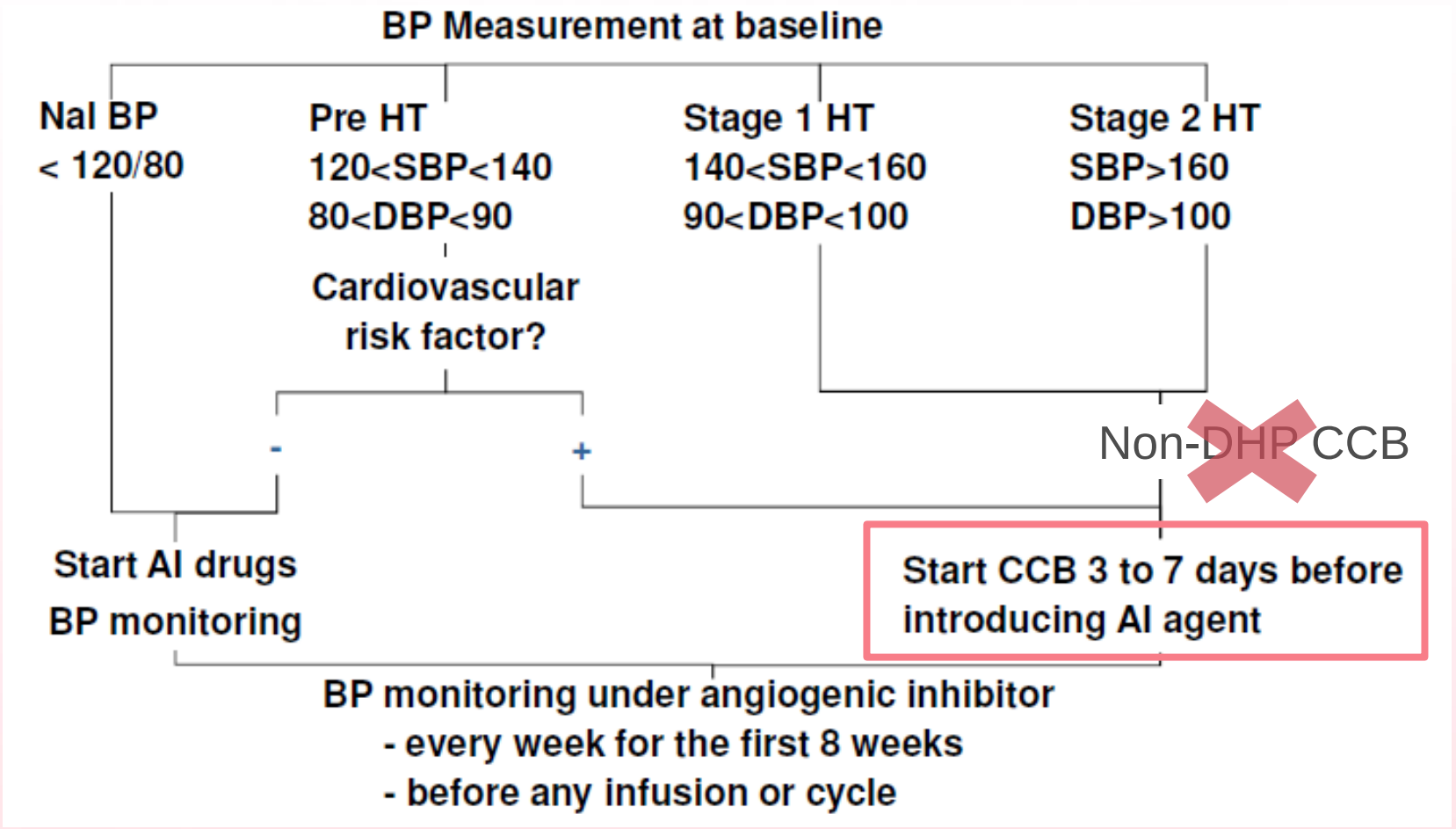


Avastin® (bevacizumab)

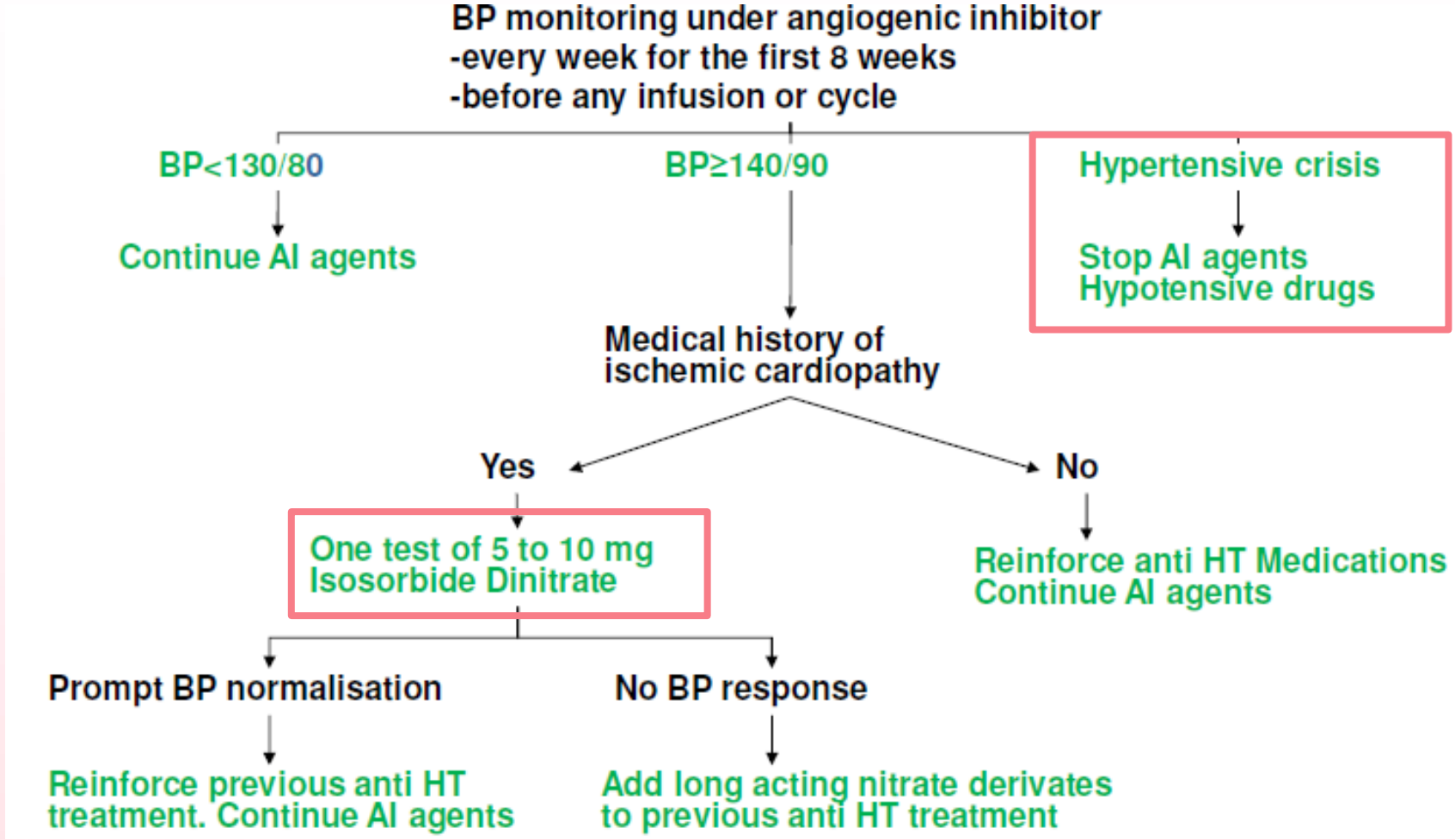
- Severe HT (>200/100mmHg) > 3-5 fold
- Overall incidence of HTN 32%
- 1% Hypertensive crisis

- BRiTE trial
- De Novo HTN 22%, worsening HT in 18.7%

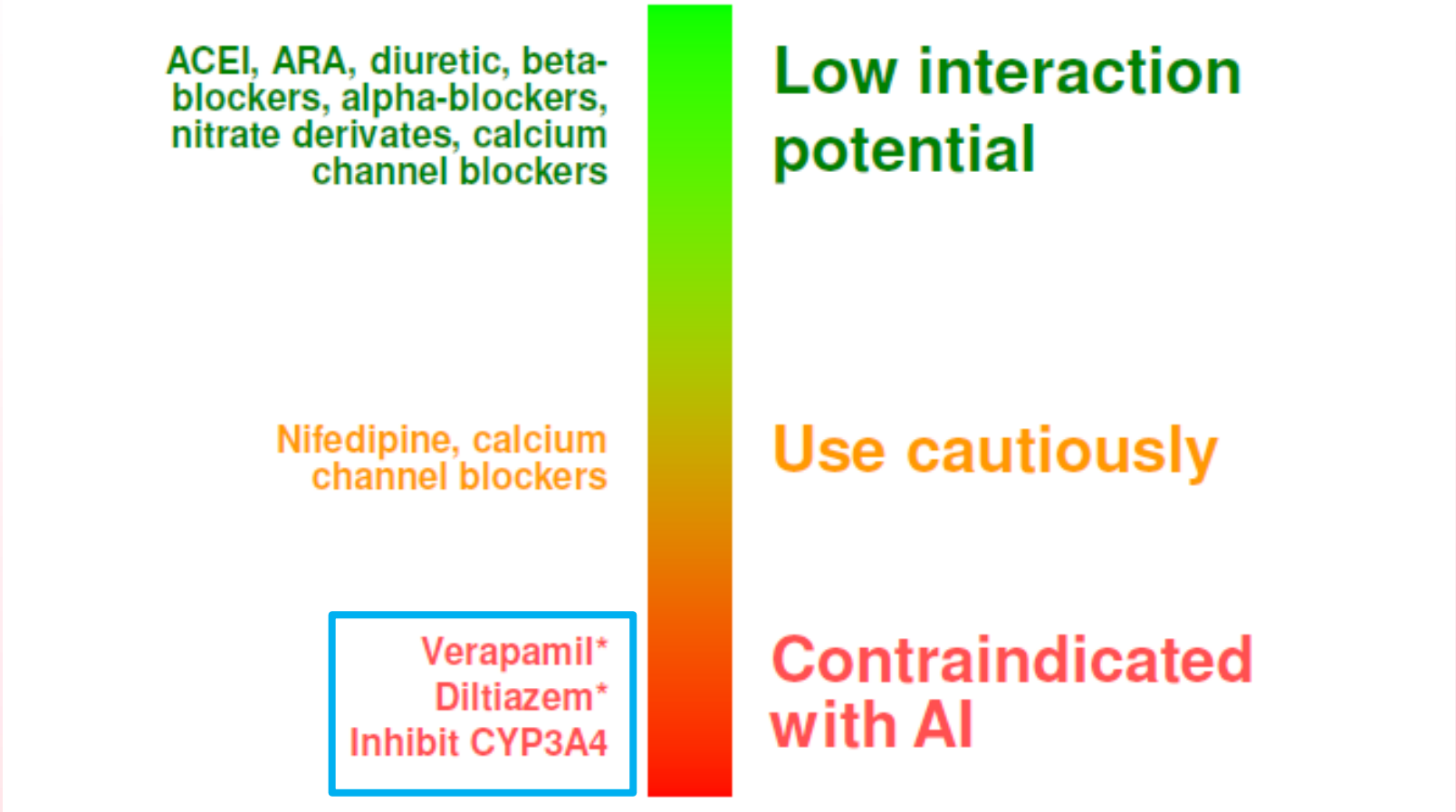
Management of HTN before VEGF inhibitor



Management of HTN after VEGF inhibitor

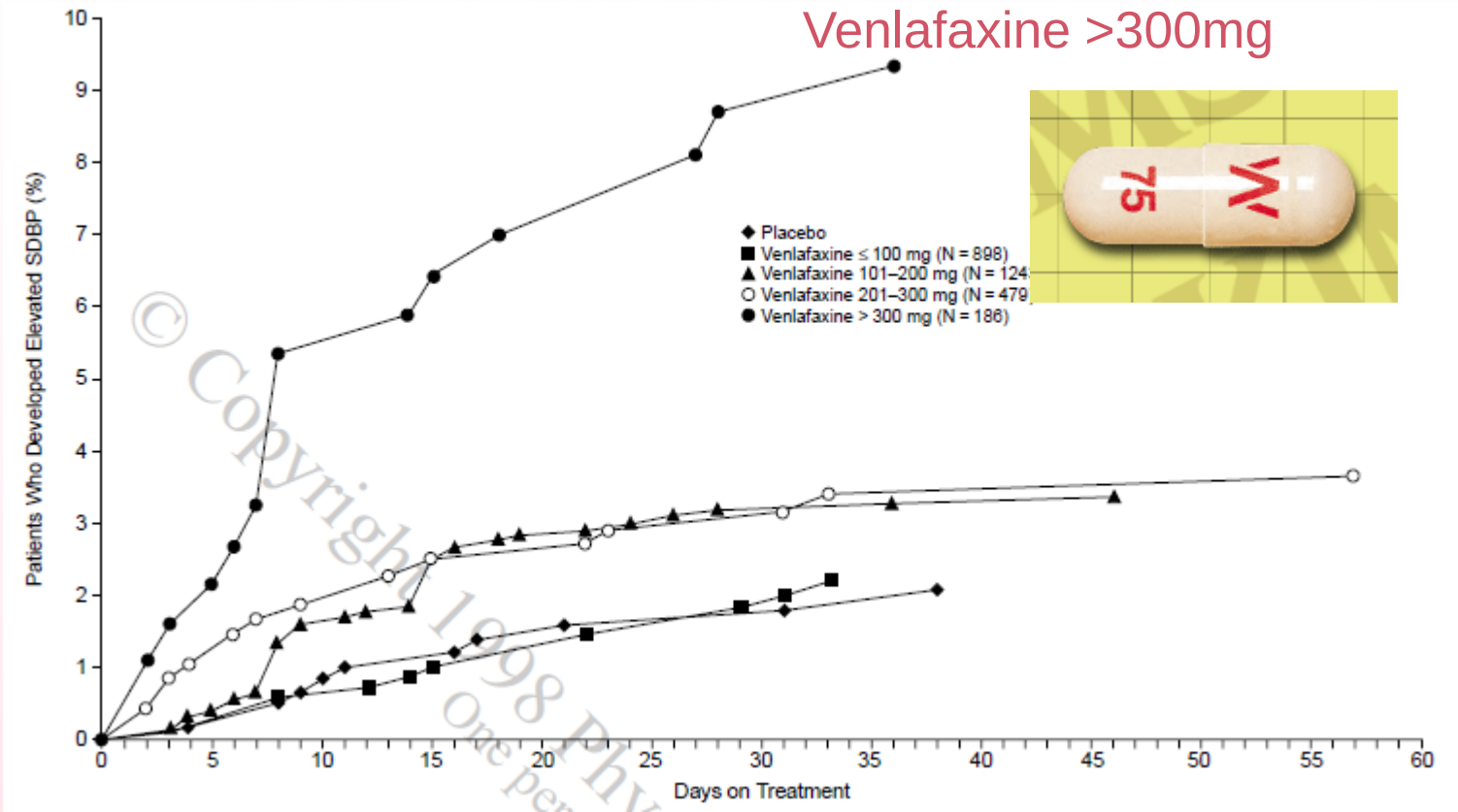


Drug interaction with VEGF inhibitor



Miscellaneous

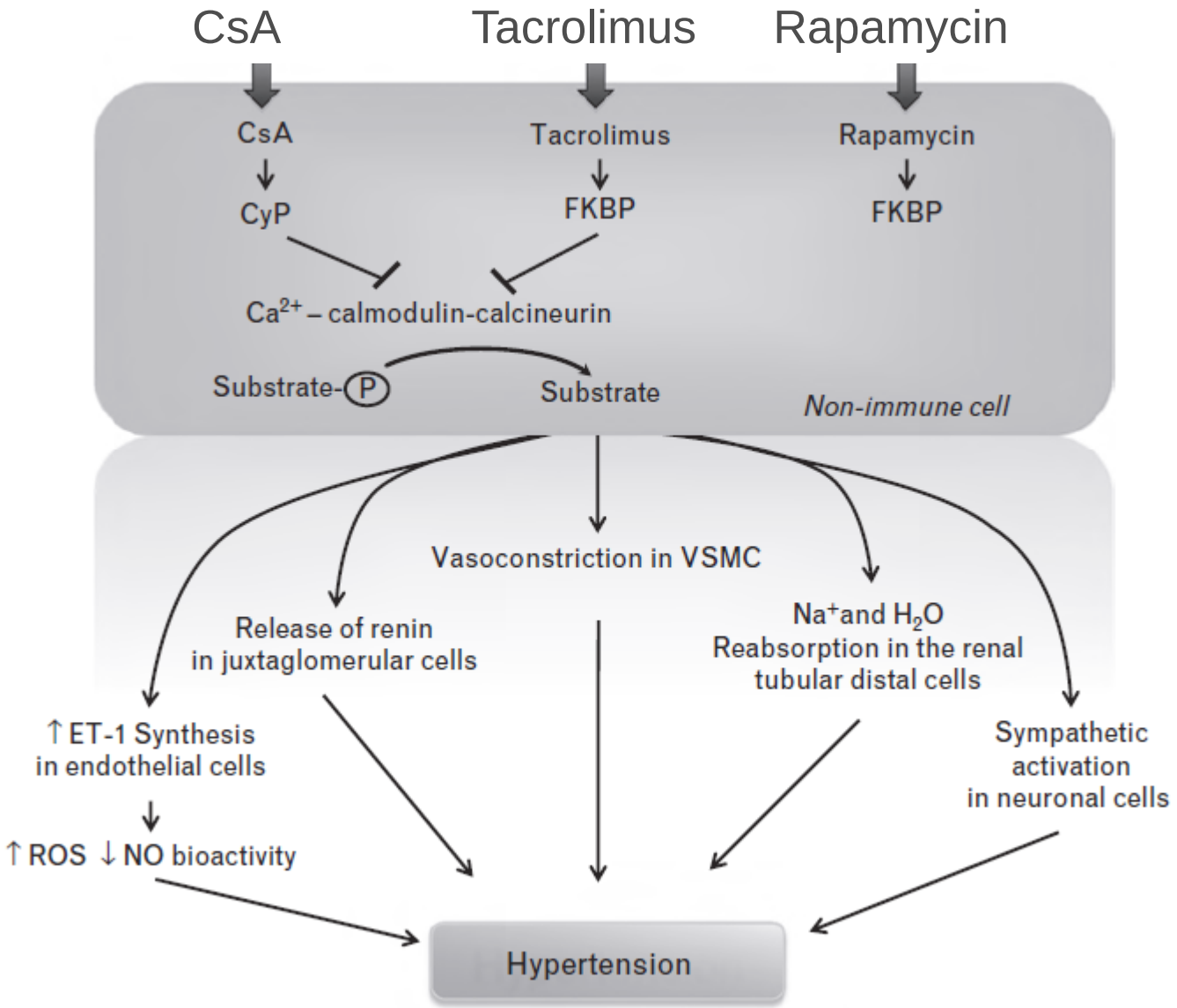
Effect of venlafaxine(Effexor®) on BP



Thase J Clin Psychiatr 1998

Antidepressant and BP

- Activation of SNS
- MAO inhibitor
- Seleglinide : Parkinson’s disease
- TCA : common in panic disorder
- Buspirone: dose dependently BP ↑
- Fluoxetine


CsA
Tacrolimus
Rapamycin
CsA
Tacrolimus
Rapamycin
CyP
FKBP
FKBP
Ca2+ – calmodulin-calcineurin
Substrate-P
Substrate
Non-immune cell
Vasoconstriction in VSMC
Release of renin in juxtaglomerular cells
Na+and H2O Reabsorption in the renal tubular distal cells
↑ ET-1 Synthesis in endothelial cells
Sympathetic activation in neuronal cells
↑ ROS ↓ NO bioactivity
Hypertension

Summary

Mechanism	Drugs	Comment
Volume retenion	Glucocorticoid	Diuretics
	Mineralocorticoid	anti-aldosterone
	Sex hormone (RAAS)	Stop OCs
	NSAIDs	CCB
SNS activation	Venlafaxine	>300mg
	Buspirone	
	PPA, pseudoephedrine	Decongestant
RAAS activation	Immune supressant	
	CETP inhibitor	Torcetrapid
Combined mechanism	VEGF inhibitor	CCB, nitrate
	EPO	
	Acetaminophen	

Thank you for your attention !