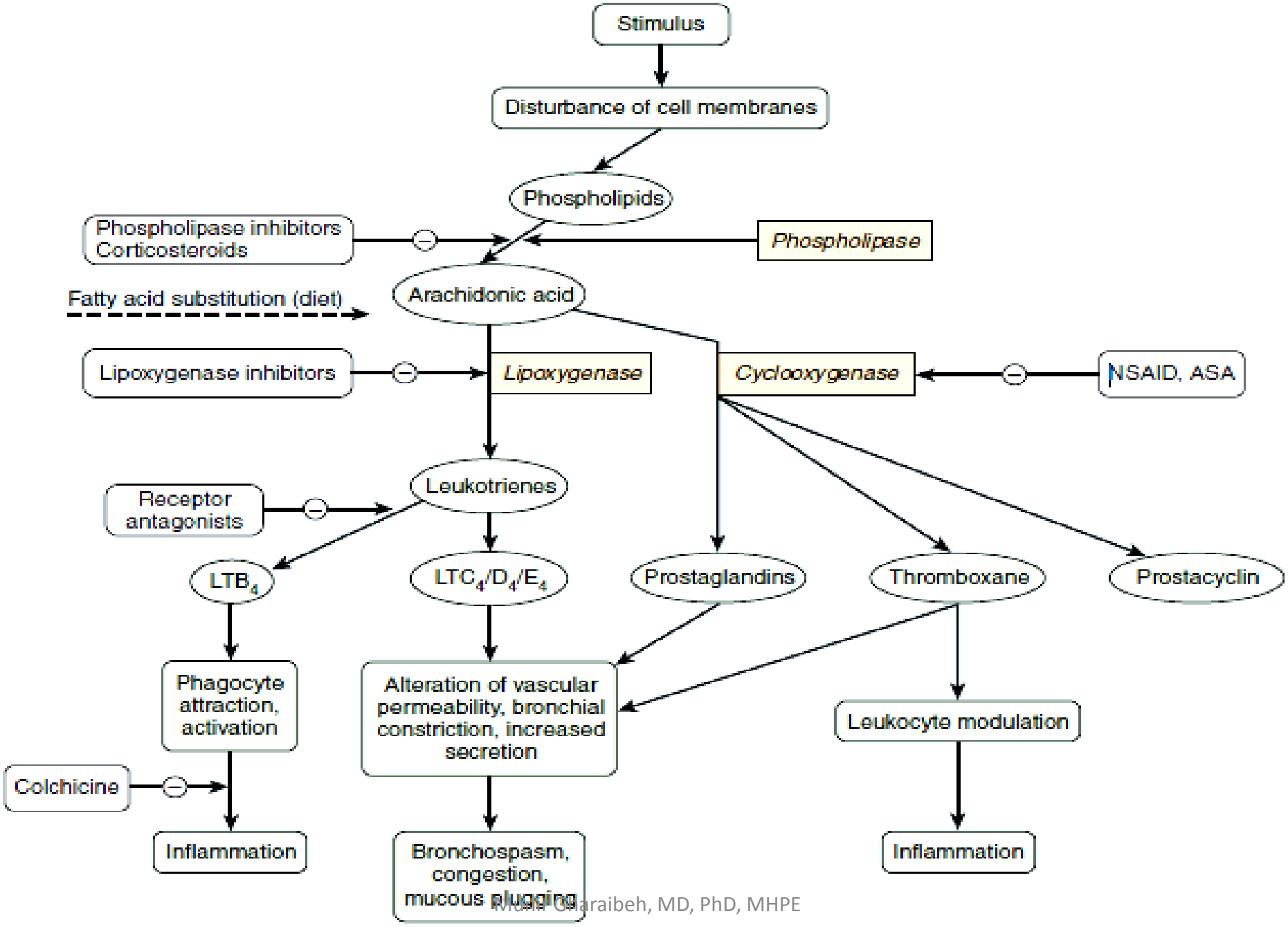
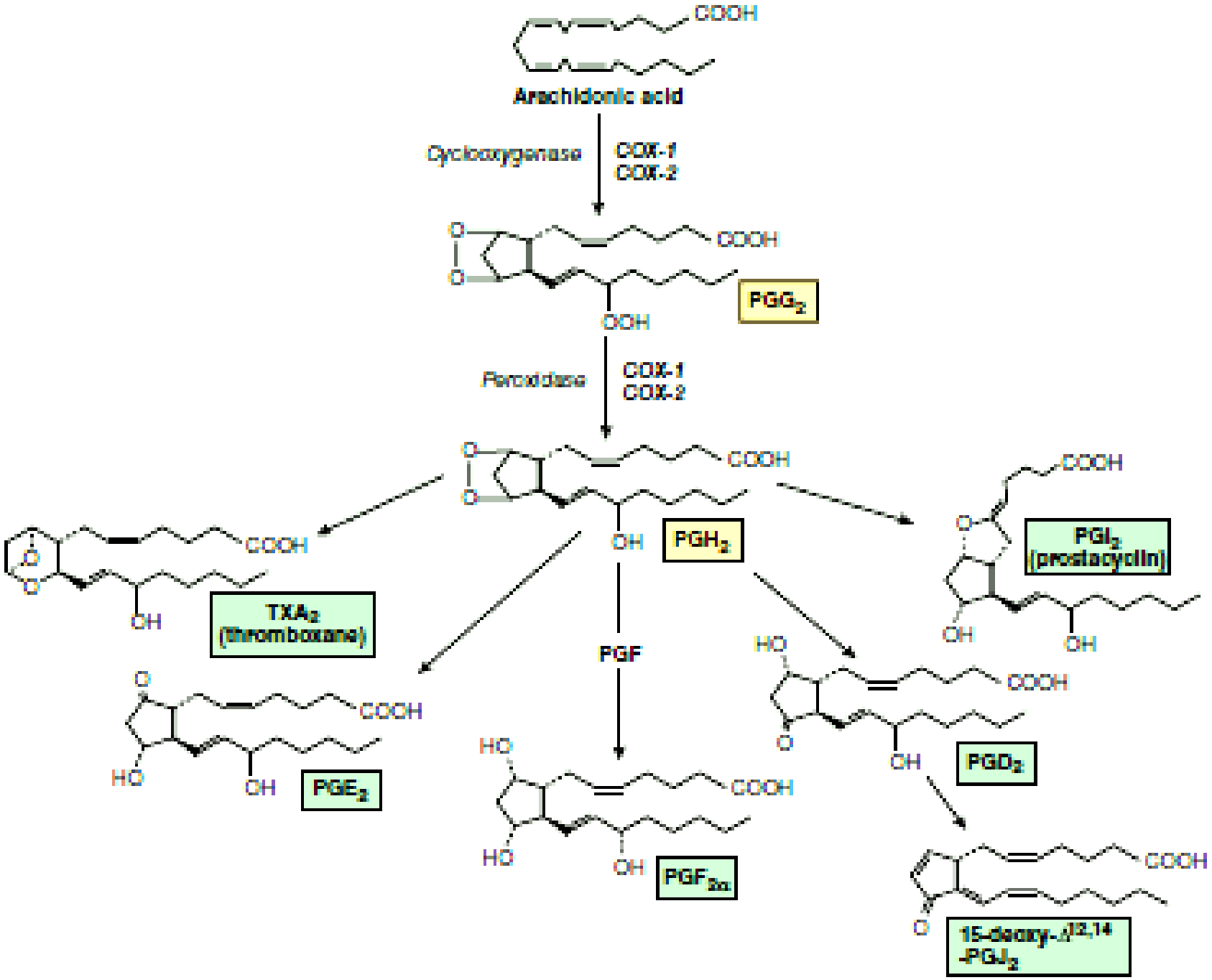
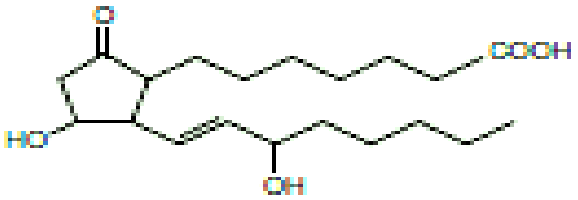
Ecosanoids

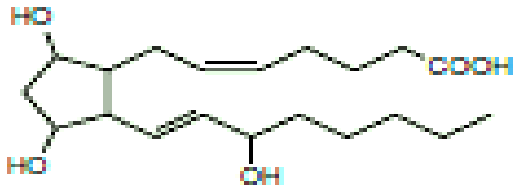
- **Prostaglandins.**
- **Thromboxanes.**
- **Leukotrienes.**


Stimulus
Disturbance of cell membranes
Phospholipids
Phospholipase inhibitors
Corticosteroids
Phospholipase
Fatty acid substitution (diet)
Arachidonic acid
Lipoxygenase inhibitors
Lipoxygenase
Cyclooxygenase
NSAID, ASA
Leukotrienes
Receptor antagonists
LTB4
LTC4/D4/E4
Prostaglandins
Thromboxane
Prostacyclin
Phagocyte attraction, activation
Alteration of vascular permeability, bronchial constriction, increased secretion
Leukocyte modulation
Colchicine
Inflammation
Bronchospasm, congestion, mucous plugging
Inflammation

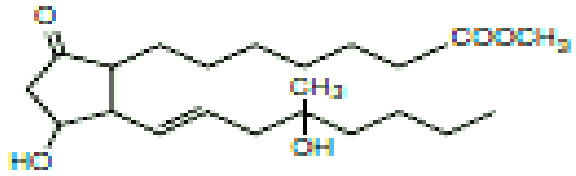

COOH
Arachidonic acid
Cyclooxygenase
COX-1
COX-2
COOH
OOH
PGG2
Peroxidase
COX-1
COX-2
COOH
OH
PGH2
COOH
OH
TXA2
(thromboxane)
COOH
HO
OH
PGE2
PGF
HO
HO
COOH
OH
PGF2α
COOH
OH
PGI2
(prostacyclin)
HO
COOH
O
OH
PGD2
COOH
O
15-deoxy-Δ12,14
-PGJ2



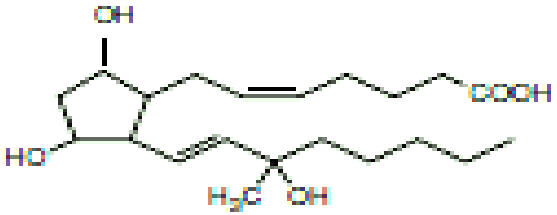
Alprostadil
(prostaglandin E_1)



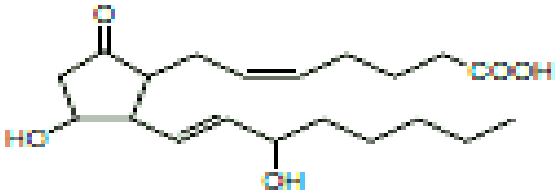
Prostaglandin $F_{2\alpha}$
($PGF_{2\alpha}$)



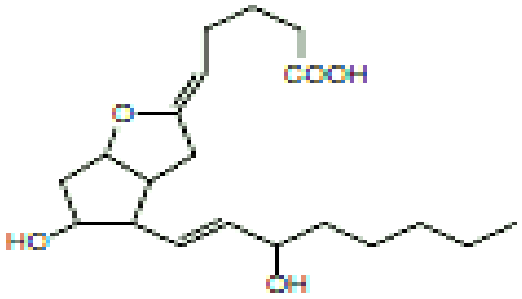
Misoprostol
(prostaglandin E_1 analog)



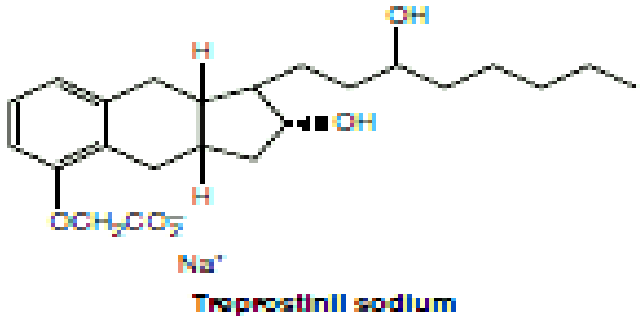
Carboprost tromethamine
(prostaglandin $F_{2\alpha}$ analog)



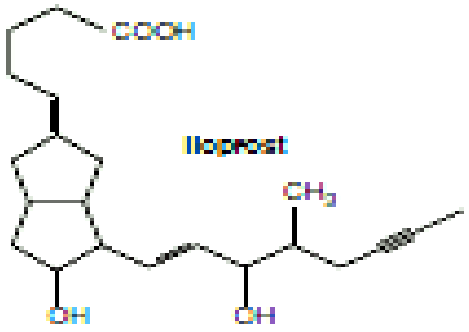
Dinoprostone
(prostaglandin E_2, PGE_2)



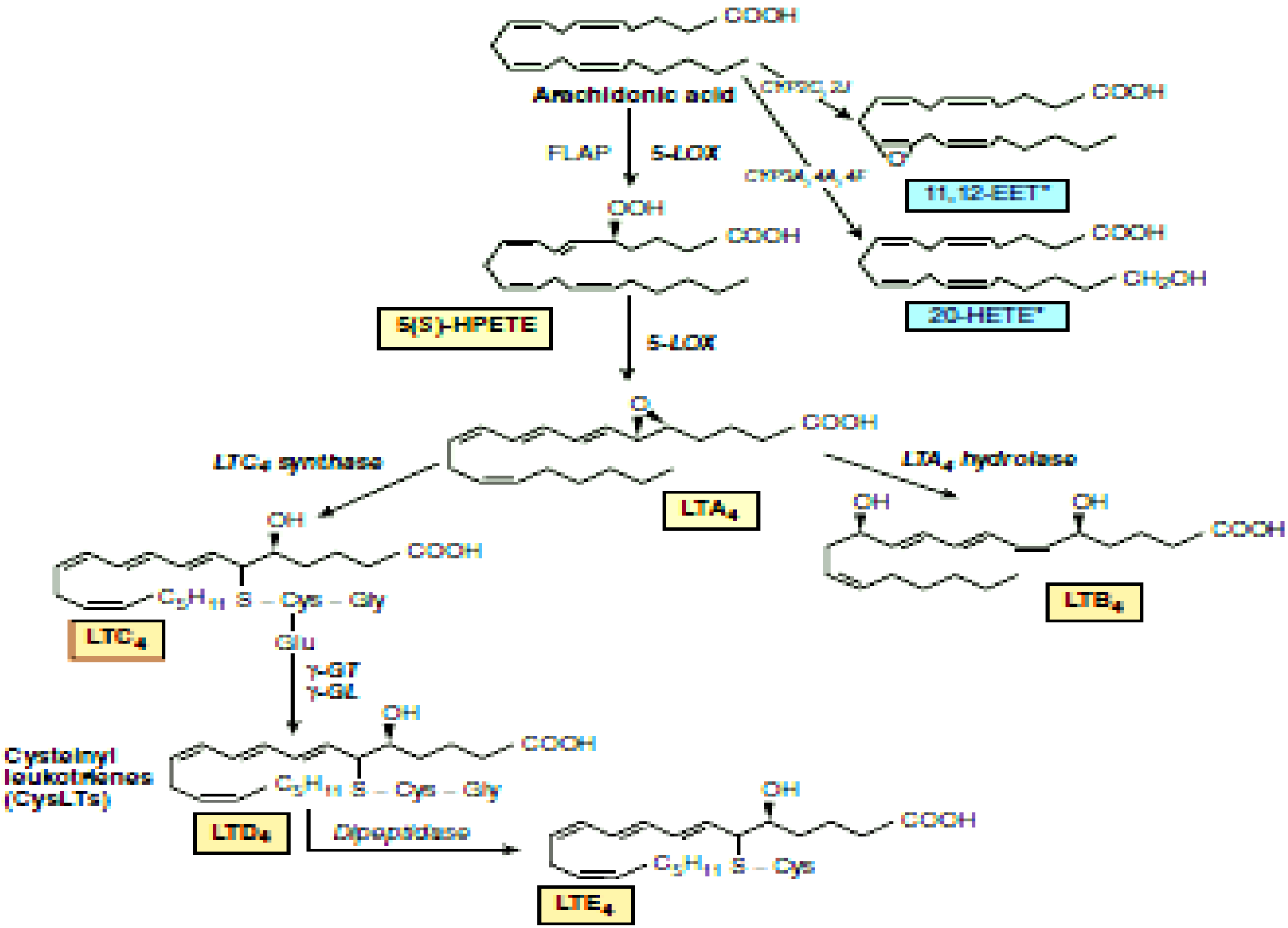
Epoprostenol
(prostacyclin, PGI_2)



Treprostinil sodium



Iloprost


COOH
Arachidonic acid
CYP2C, 2J
COOH
O
11,12-EET*
FLAP
5-LOX
CYP3A, 4A, 4F
COOH
COOH
5(S)-HPETE
COOH
CH2OH
20-HETE*
5-LOX
O
COOH
LTC4 synthase
LTA4 hydrolase
LTA4
OH
COOH
OH
OH
COOH
C5H11 S – Cys – Gly
LTC4
LTB4
Glu
γ-GT
γ-GL
OH
COOH
Cysteinyl leukotrienes (CysLTs)
C5H11 S – Cys – Gly
LTD4
Dipeptidase
OH
COOH
C5H11 S – Cys
LTE4

Vasoactive Peptides

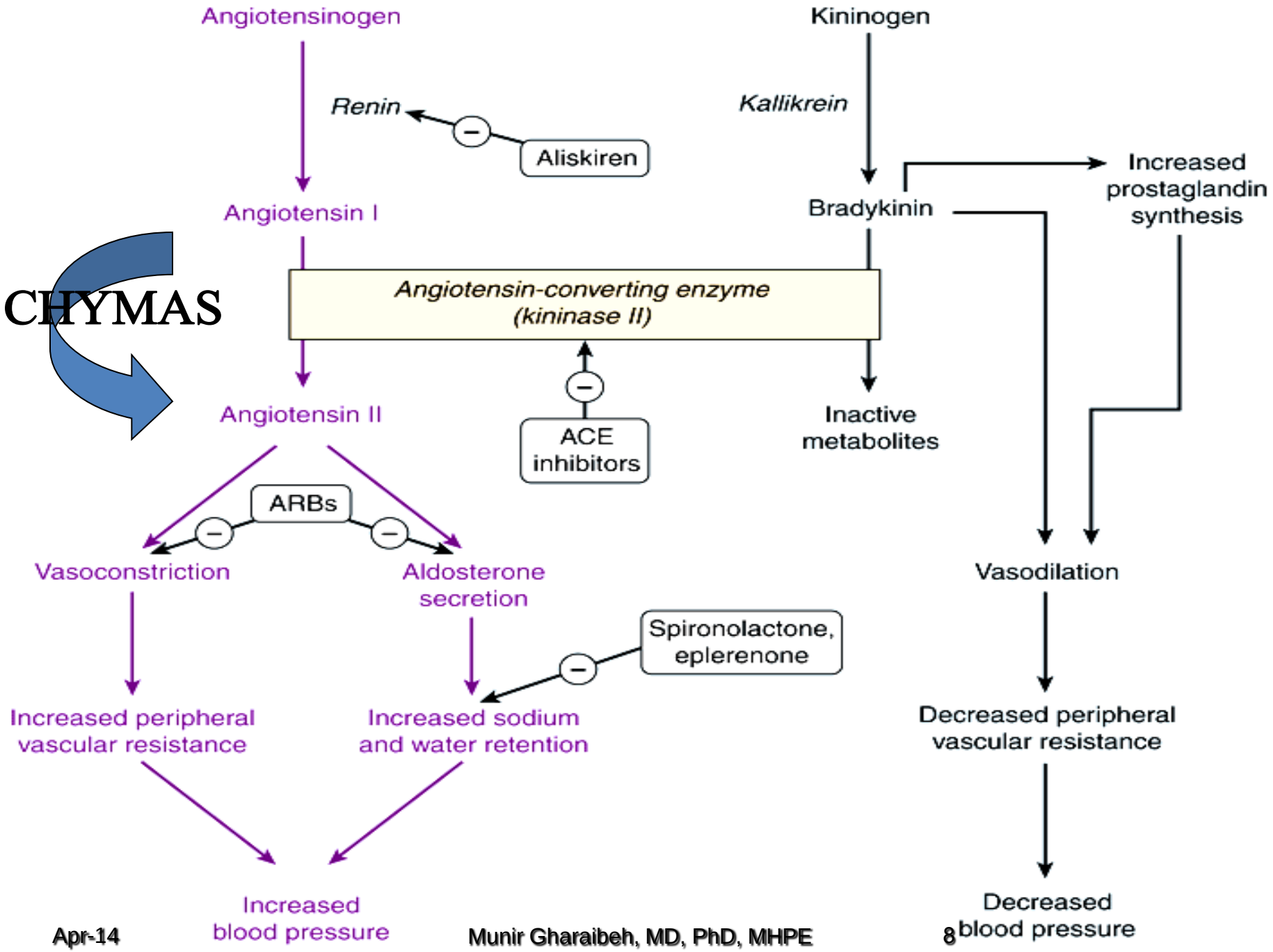
- **Angiotensin.**
- **Kinins.**
- **Vasopressin.**
- **Natriuretic Peptides.**
- **Endothelins.**
- **Vasoactive Intestinal Peptide.**
- **Subtance P.**
- **Neurotensin.Calctonin Gene-Related Peptide.**
- **Adrenomedullin.**
- **Neuropeptide Y**
- **Urotensin.**

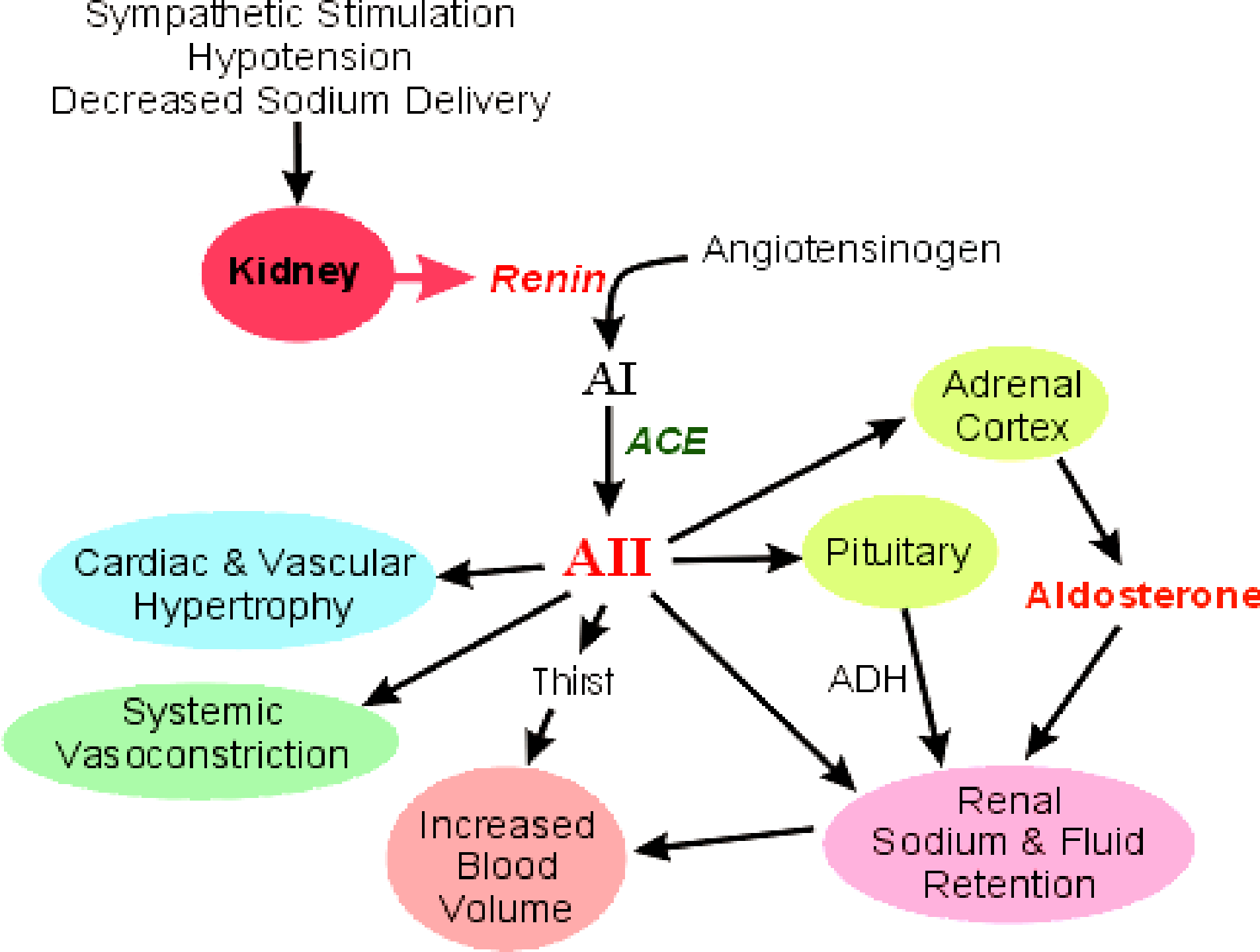
What is RAAS?

The renin-angiotensin aldosterone system (RAAS) is a hormonal cascade that functions to control arterial pressure, tissue perfusion, and extracellular volume.

Pathophysiologic processes might occur when components of the RAAS are **overexpressed or inhibited**, thus disturbing the balance of this regulatory system

Dysregulation of the RAAS plays an important role in the pathogenesis of cardiovascular and renal disorders.


Angiotensinogen
Renin
Aliskiren
Angiotensin I
CHYMAS
Angiotensin-converting enzyme
(kininase II)
Angiotensin II
ACE
inhibitors
ARBs
Vasoconstriction
Aldosterone
secretion
Spironolactone,
eplerenone
Increased peripheral
vascular resistance
Increased sodium
and water retention
Increased
blood pressure
Kininogen
Kallikrein
Bradykinin
Increased
prostaglandin
synthesis
Inactive
metabolites
Vasodilation
Decreased peripheral
vascular resistance
Decreased
blood pressure


Sympathetic Stimulation
Hypotension
Decreased Sodium Delivery
Kidney
Renin
Angiotensinogen
AI
ACE
Adrenal Cortex
Cardiac & Vascular Hypertrophy
AII
Pituitary
Aldosterone
Thirst
ADH
Systemic Vasoconstriction
Increased Blood Volume
Renal Sodium & Fluid Retention

Local Renin-angiotensin Systems

- **The renin-angiotensin system is a classic endocrine system.**
- **There are complete local renin-angiotensin systems existing entirely within organs and tissues .**

e.g in the vascular endothelium, volume depletion increases angiotensinogen levels in aortic smooth muscle.

-Then either locally produced or systemic renin could initiate the sequential formation of angiotensin I and II.

The Cardiac Renin-Angiotensin System

-Stretch directly increases:

Release of angiotensin II from cardiac myocytes.

Expression of the angiotensinogen gene on the long-term.

-The apparent function of the cardiac RAAS is to maintain cellular balance of inhibition and cellular growth .

Effect of the Angiotensin II on the heart

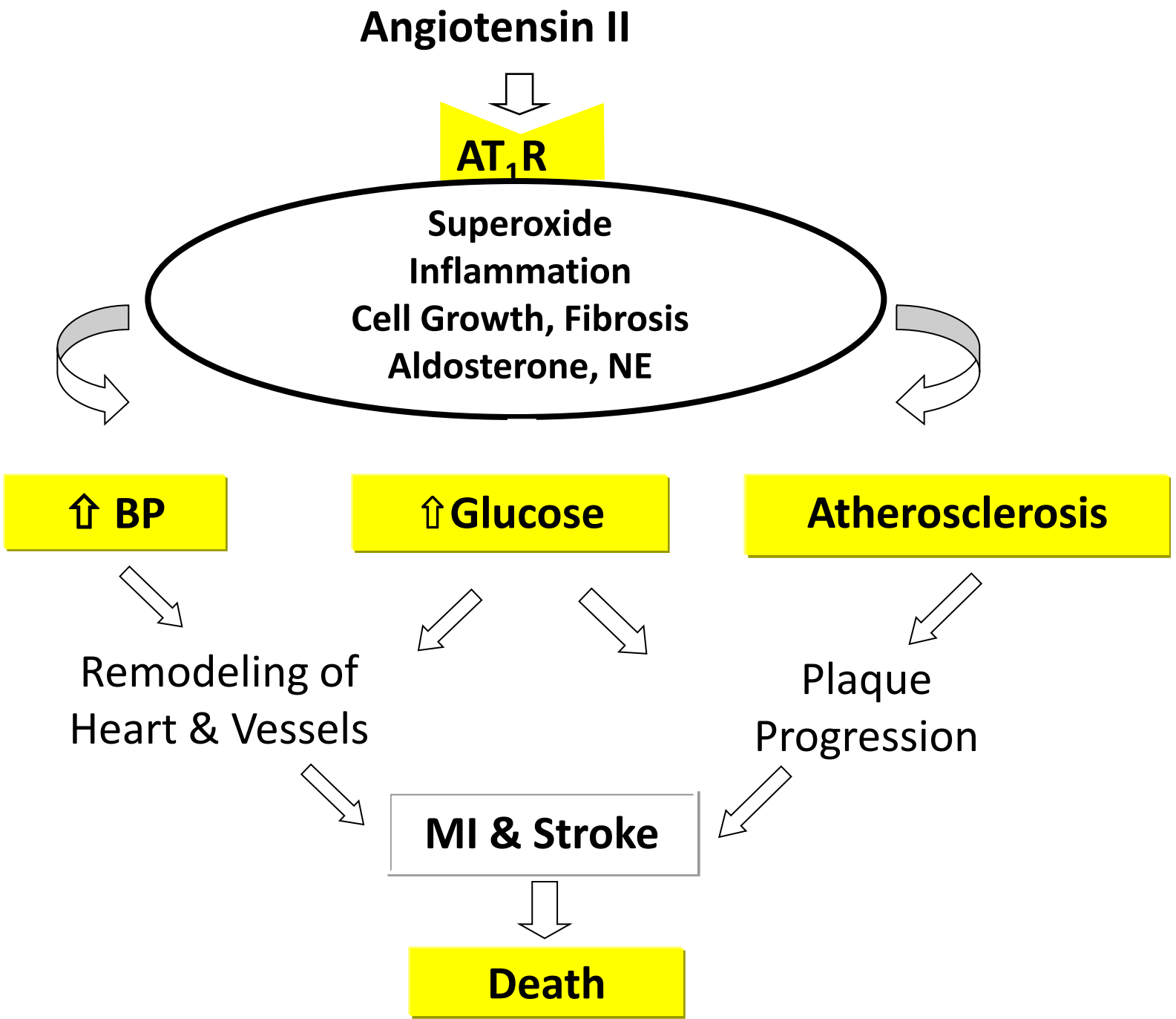
1- **Inotropy .**

2- Hypertrophy.

3- Ventricular remodeling

4- Electrical remodeling.

5- Pathogenesis of atherosclerosis

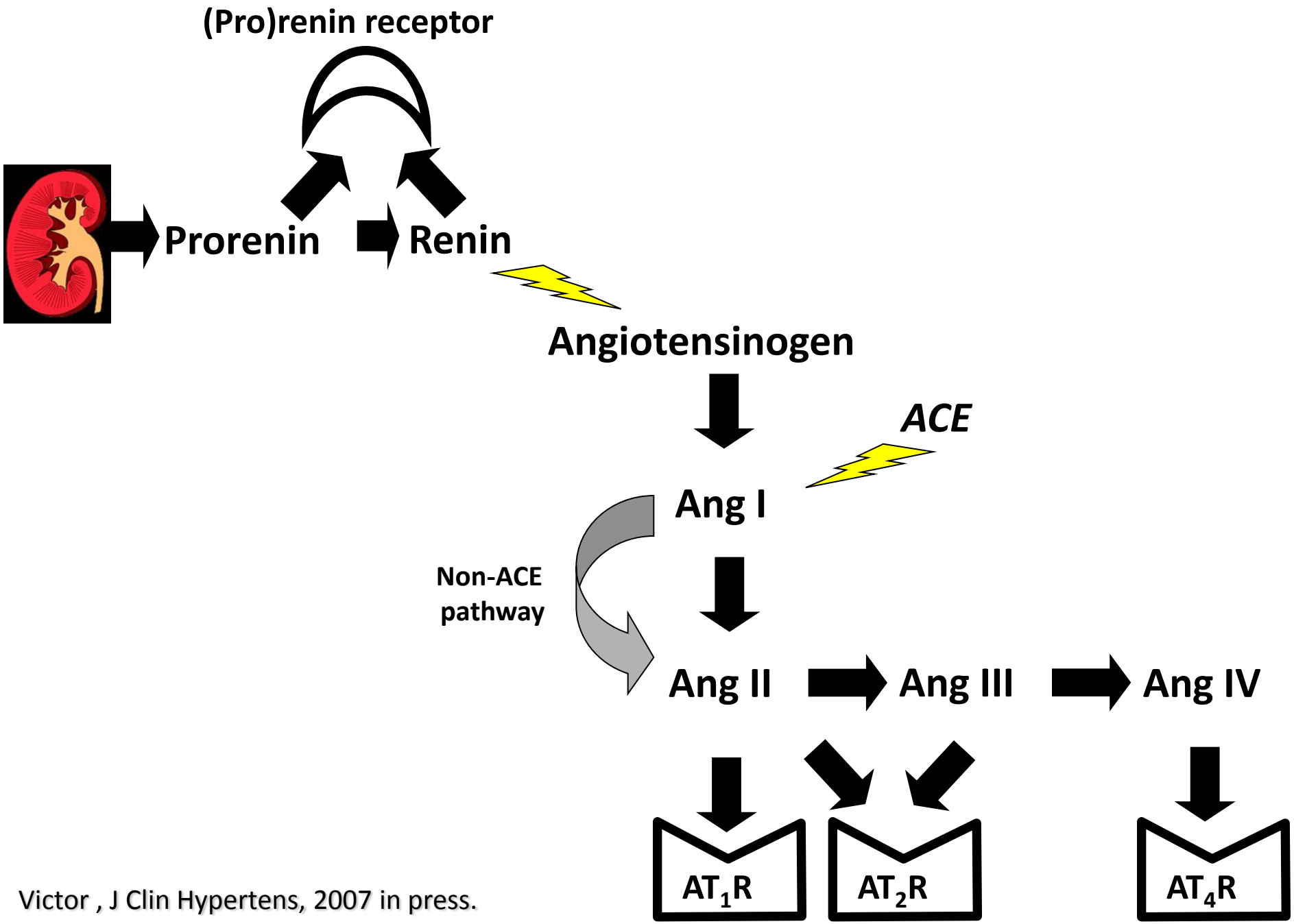

Angiotensin II
AT1R
Superoxide
Inflammation
Cell Growth, Fibrosis
Aldosterone, NE
⇧ BP
⇧Glucose
Atherosclerosis
Remodeling of
Heart & Vessels
Plaque
Progression
MI & Stroke
Death

Alternative Pathways Of The Renin

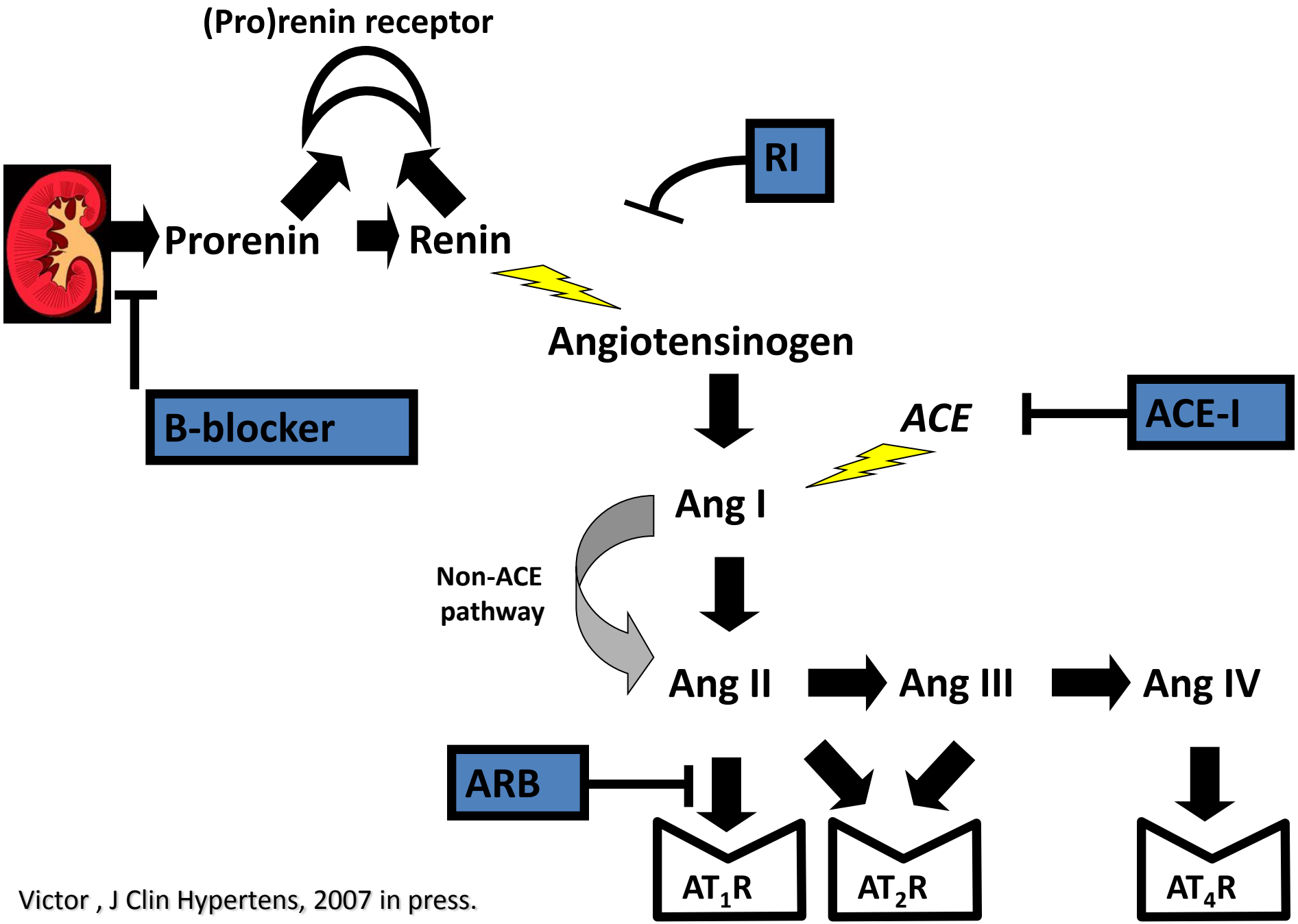
Angiotensin System : Alternative enzymatic pathways not involving ACE contribute to angiotensin II production

Human heart chymase appears to be the most important of these pathways, particularly in the ventricles .

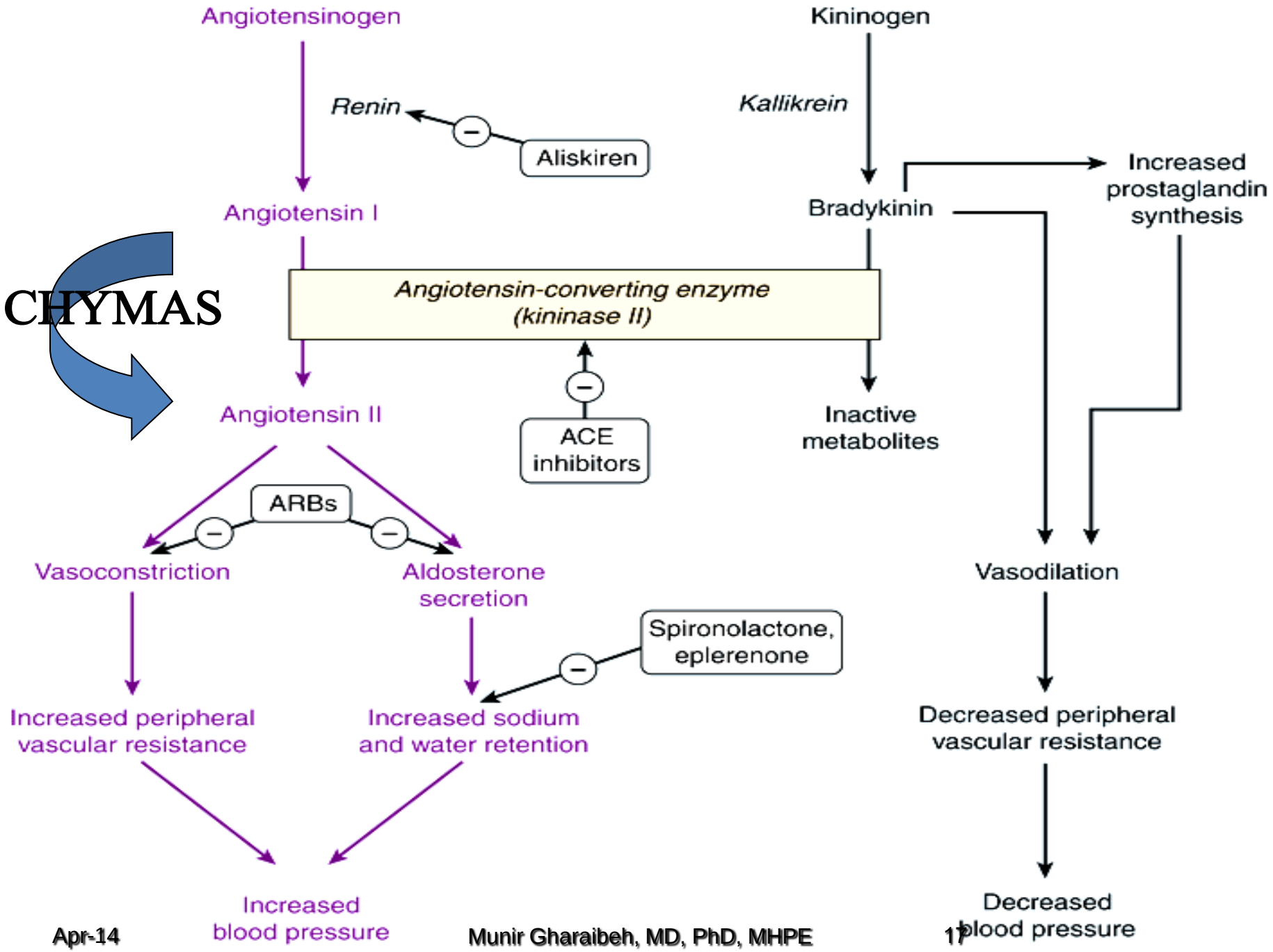
The physiologic importance of chymase is uncertain because of the presence of natural protease inhibitors in the interstitial fluid which inhibit chymase-induced angiotensin II production.



Victor , J Clin Hypertens, 2007 in press.



Victor , J Clin Hypertens, 2007 in press.


Angiotensinogen
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Angiotensin II
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vascular resistance
Increased sodium
and water retention
Increased
blood pressure
Kininogen
Kallikrein
Bradykinin
Increased
prostaglandin
synthesis
Inactive
metabolites
Vasodilation
Decreased peripheral
vascular resistance
Decreased
blood pressure

Direct Renin Inhibitors

The most recent class of agents that block the RAAS to be introduced are the direct renin inhibitors represented by **aliskiren**,

which was recently approved for treatment of hypertension.

This compound differs from the ACEIs and ARBs in that, by blocking the catalytic activity of renin at the point of activation of the RAAS, it blocks the synthesis of all angiotensin peptides and prevents the compensatory increase in renin activity

Angiotensin-converting enzyme inhibitors (ACEI)

- **ACEI lower systemic vascular resistance and venous pressure, and reduce levels of circulating catecholamines, thus improving myocardial performance.**

Cardiorenal Effects of ACE Inhibitors

- Vasodilation (arterial & venous)
  - reduce arterial & venous pressure
  - reduce ventricular afterload & preload
- Decrease blood volume
  - natriuretic
  - diuretic
- Depress sympathetic activity
- Inhibit cardiac and vascular hypertrophy

Angiotensin - Converting Enzyme Inhibitors (ACEI)

Therapeutic Benefits:

- High-rennin hypertension (20%).
- HF and Ischemic Heart Disease.
- Do not increase HR.
- Diabetic Nephropathy, dilate efferent arterioles which reduces intraglomerular pressure and consequently protects against progressive glomerulosclerosis.
- No need for a diuretic but can be added.
- Can be combined with CCBs.
- Should not be combined with Beta blockers, except in HF.
- No metabolic effects .

Angiotensin - Converting Enzyme Inhibitors (ACEI)

Side Effects:

Captopril is SH containing drug, so very toxic(bone marrow suppression, disguesia, proteinuria, allergic skin rash, fever)

- **Hypotension(*First Dose Phenomena*) especially with renovascular hypertension.**
- **K+ retention, especially in the presence of renal dysfunction or when combined with K+ sparing diuretics or ARBs.**
- **Cough(10% of patients).**
- **Angioedema.**

Angiotensin-converting enzyme inhibitors ACEI

- **Captopril**
- **Benazepril**
- **Enalapril**
- **Fosinopril**
- **Lisinopril**
- **Moexipril**
- **Quinapril**
- **Ramipril**

Angiotensin receptor antagonists(ARBs)

Losartan.

Irbersartan.

Candesartan.

Valsartan

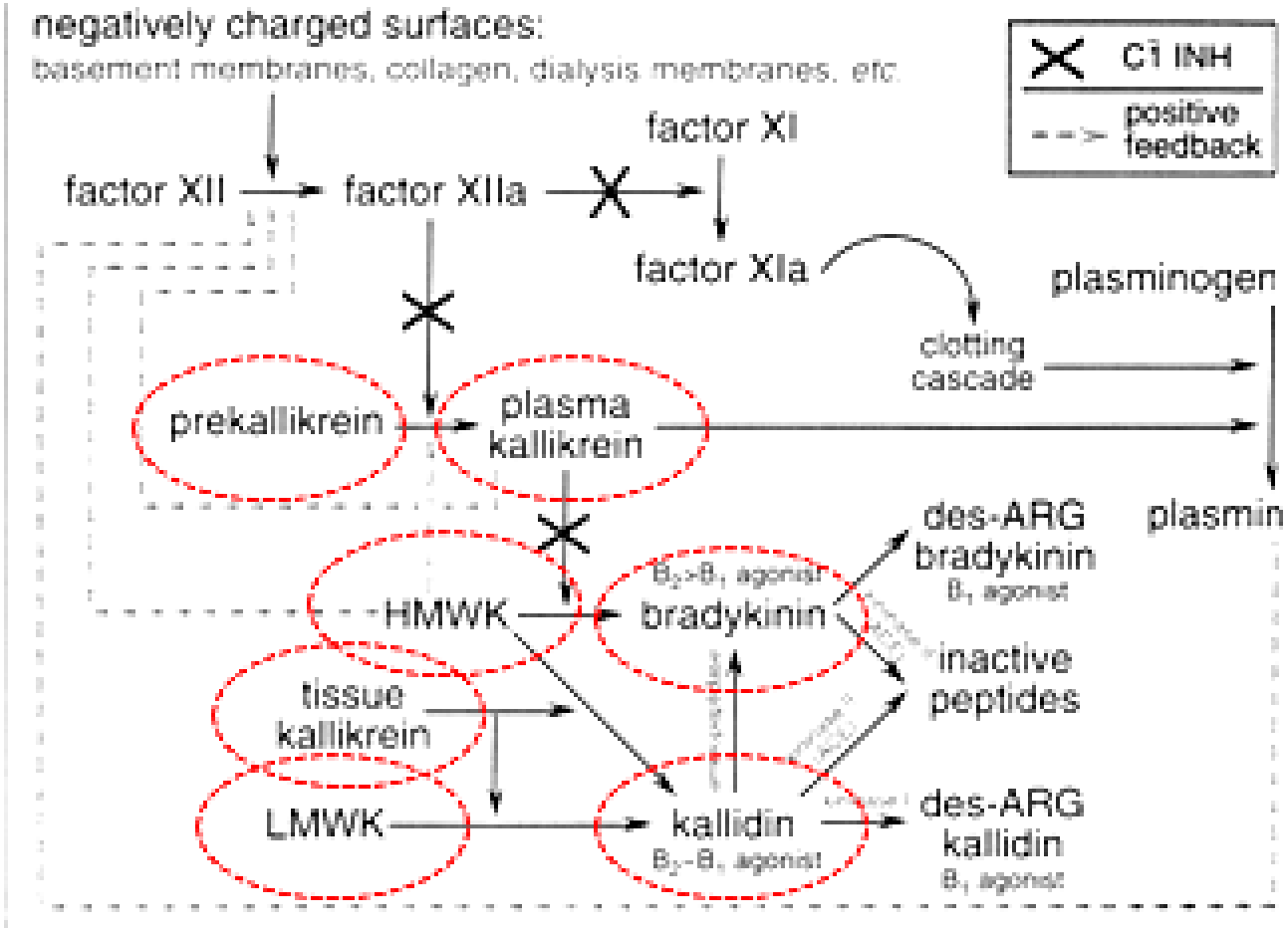
Have similar haemodynamic effects to ACEI

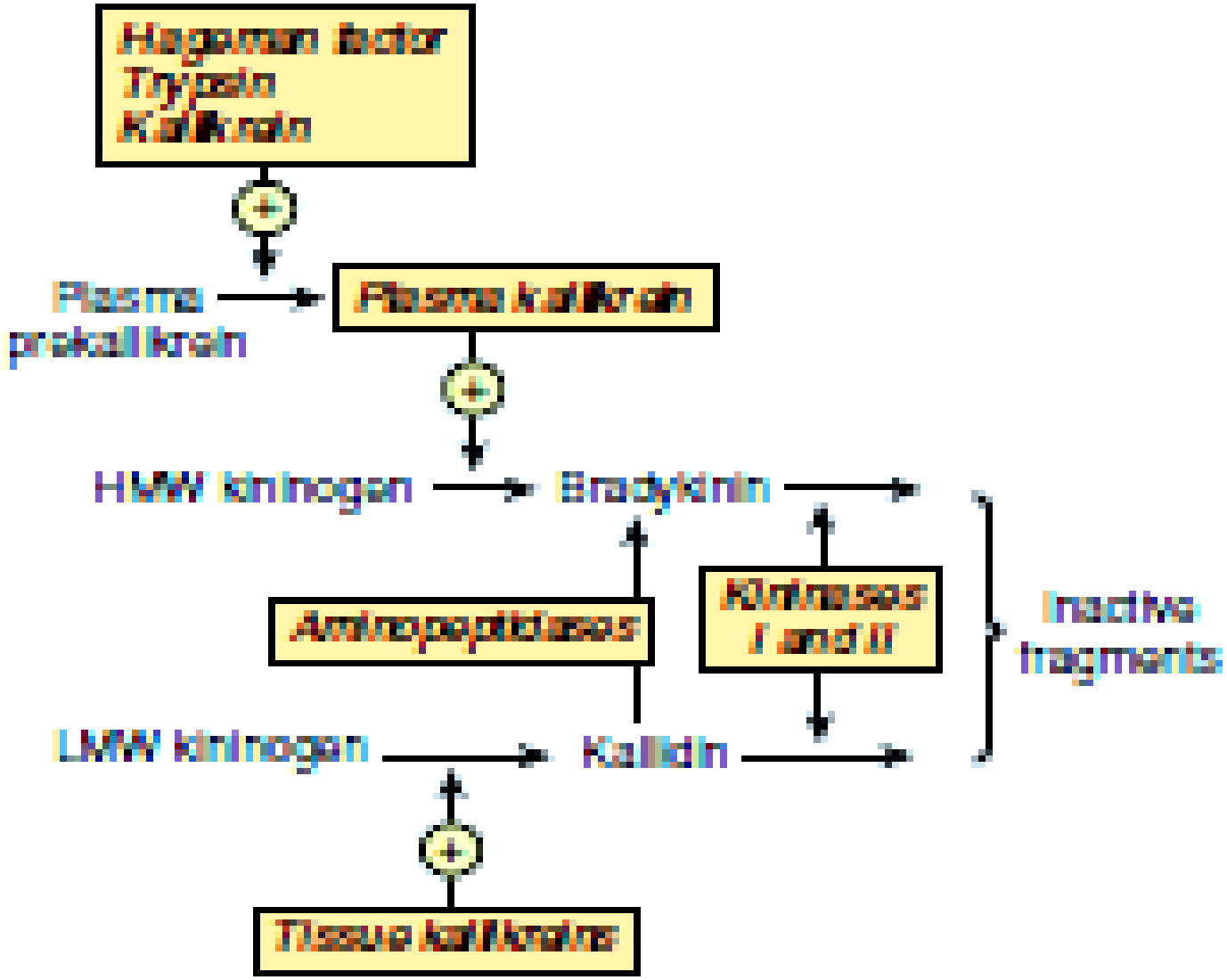
Do not affect bradykinin metabolism.

Do not cause cough.

Block the effect of Angiotensin II generated from both pathways (chymas &ACE)

Kallikrein Kinin System




Hageman factor
Trypsin
Kallikrein
Plasma prekallikrein
Plasma kallikrein
HMW kininogen
Bradykinin
Aminopeptidases
Kininases I and II
Inactive fragments
LMW kininogen
Kallidin
Tissue kallikrein

Kinin Actions

Cardiovascular System:

- Arteriolar vasodilation: direct & endothelium-dependent via the release of NO and PGI_2
- Venous constriction: direct and via $PGF_{2\alpha}$
- Increased capillary permeability
- Response to iv bradykinin:
  - Transient decrease in BP: direct arteriolar dilation
  - Restoration of normal BP: reflex sympathetic discharge

Kinin Actions

Other Effects::

- Pro-inflammatory
- Algesic: via PGE_2
- Constrict visceral smooth muscle

Putative Effects::

- Local modulators of blood flow
- Modulate tone of salivary and pancreatic ducts
- Regulate transport of H_2O, electrolytes, aa in GIT

Kinin Receptors

B_1:

- Sensitive to des-Arg metabolites
- Kallidin is 10x more potent than BK
- limited tissue distribution
- VSM contraction, proliferation,
- Collagen synthesis, inflammation
- Induced by trauma

B_2 (B_{2A}, B_{2B}):

- Sensitive to intact peptides
- GPCR; wide tissue distribution
- Vasodilation, permeability, pain.
- Ca^{++} mobilization, Cl^- transport, NO, PLC, PLA_2, AC

B_3: Unknown function

Kinins

Table 25–2
Structure of Kinin Agonists and Antagonists, Listed from Carboxyl Terminus

NAME	STRUCTURE*	FUNCTION
Bradykinin	Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg	Agonist, $B_2 > B_1$
Kallidin	Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg	Agonist, $B_2 \simeq B_1$
des-Arg^9-bradykinin	Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe	Agonist, B_1
des-Arg^{10}-kallidin	Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe	Agonist, B_1
des-Arg^9-[Leu^8]-bradykinin	Arg-Pro-Pro-Gly-Phe-Ser-Pro-Leu	Antagonist, B_1
[D-Phe^7]-bradykinin	Arg-Pro-Pro-Gly-Phe-Ser-[D-Phe]-Phe-Arg	Antagonist, B_2 (also B_1 to some extent)
HOE 140	[D-Arg]-Arg-Pro-Hyp-Gly-Thi-Ser-Tic-Oic-Arg*	Antagonist, B_2
WIN 64338	Nonpeptide	Antagonist, B_2

*Hyp, *trans*-4-hydroxy-Pro; Thi, β-(2-thienyl)-Ala; Tic, [D]-1,2,3,4-tetrahydroisoquinolin-3-yl-carbonyl; Oic, (3as,7as)-octahydroindol-2-yl-carbonyl.
SOURCE: Modified from Trifilieff *et al.*, 1993.

Kinins

Potential Clinical Uses of KKS Antagonists:

- Allergic conditions
- Anti-inflammatory
- Anti-nociceptive