Anti-hypertension Drugs

Hypertension: General Facts

- Most common cardiovascular **disease**
- About 1 in 3 Americans have **hypertension**
- Usually asymptomatic unless **end organ** damage occurs
- Diagnosis based on repeated **reproducible** measurement of elevated blood pressure
- Hypertension is a leading cause **of** stroke, heart attack, and kidney failure
- Hypertension is controllable by **life** style modification **and/or** medications

Antihypertensive amongst most prescribed drugs in top 10 for 2010

- Lisinopril was 3rd at 87 million Rxs
- Amlodipine 5th at 57 million
- Hydrochlorothiazide 10th at 48 million

Treatment of Hypertension: classification

Categories

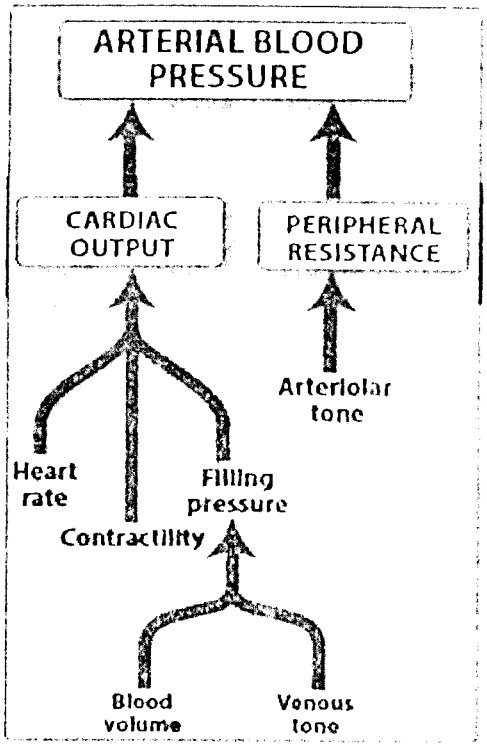
BP	Systolic	Diastolic
Normal	<120	<80
Prehypertension	120-139	80-89
Stage1	140-159	90-99
Stage2	>160	>100

Risk factors

1. Age above 55 and 65 in Men and Woman respectively
2. Family History
3. Smoking
4. DM and Dyslipidemia
5. Obesity

What is Blood Pressure ?

- Blood pressure is proportional to blood flow (**cardiac output**, CO) and resistance to the blood flowing through the vasculature (**systemic vascular resistance**, SVR)



Cardiac Output (CO)

- CO equals stroke volume times the heart rate in beats per minute
- CO increases with increasing heart rate, increasing contractility, and increasing stroke volume
- Stroke volume increases with increased venous return which increases ventricular filling pressure

Systemic Vascular Resistance(SVR)

- Resistance to blood flow through all of the systemic vasculature other than pulmonary
- SVR determined by factors affecting vascular resistance in individual vascular beds
  - Length and diameter of vessels
  - Physical characteristics of blood: viscosity
  - Extra vascular mechanical forces: muscle contraction

- Cardiac output and peripheral resistance, in turn, are controlled mainly by two overlapping control mechanisms:
- Baroreflexes and the sympathetic nervous system
- renin–angiotensin–aldosterone system

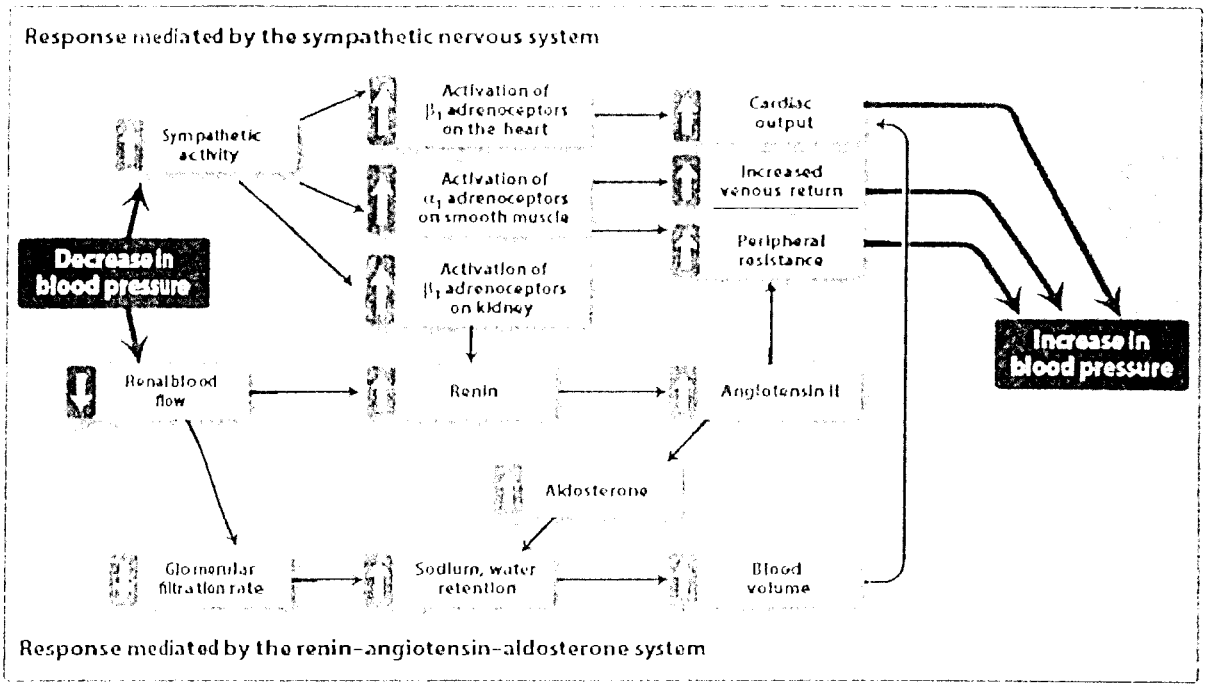
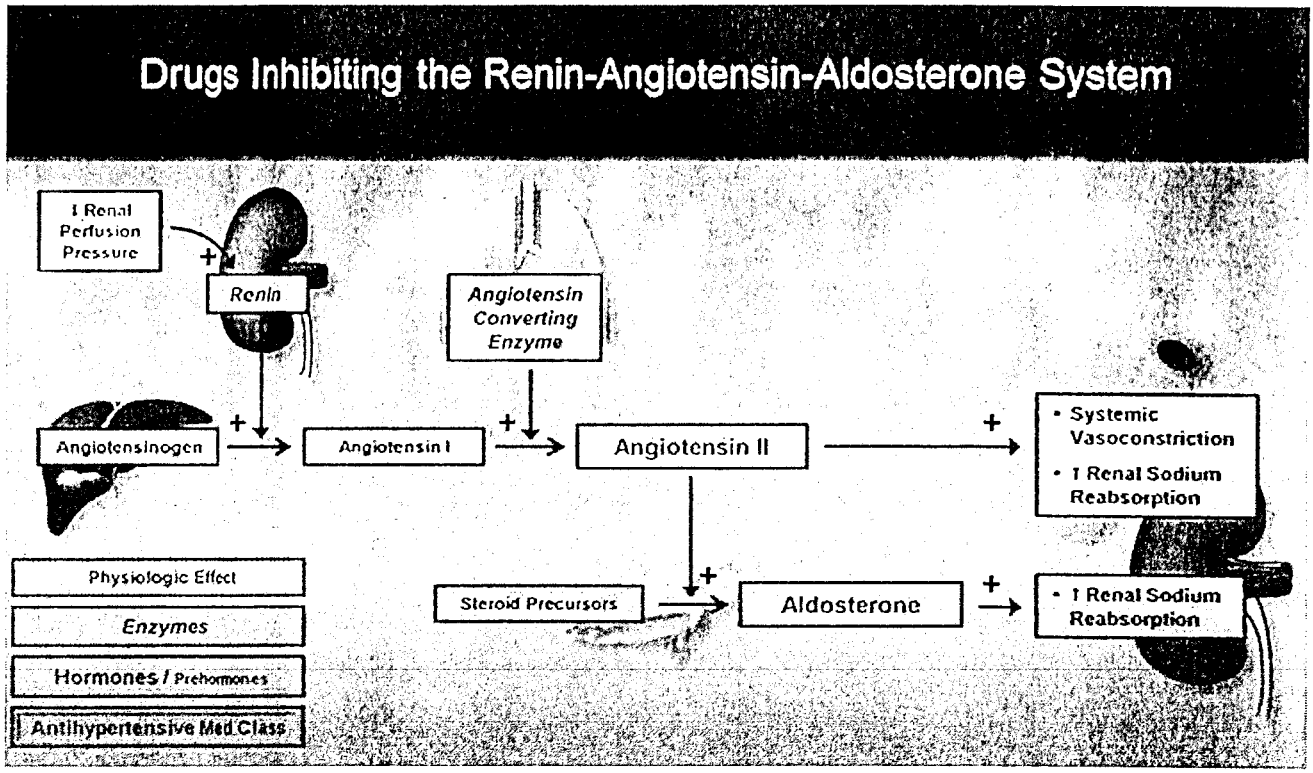
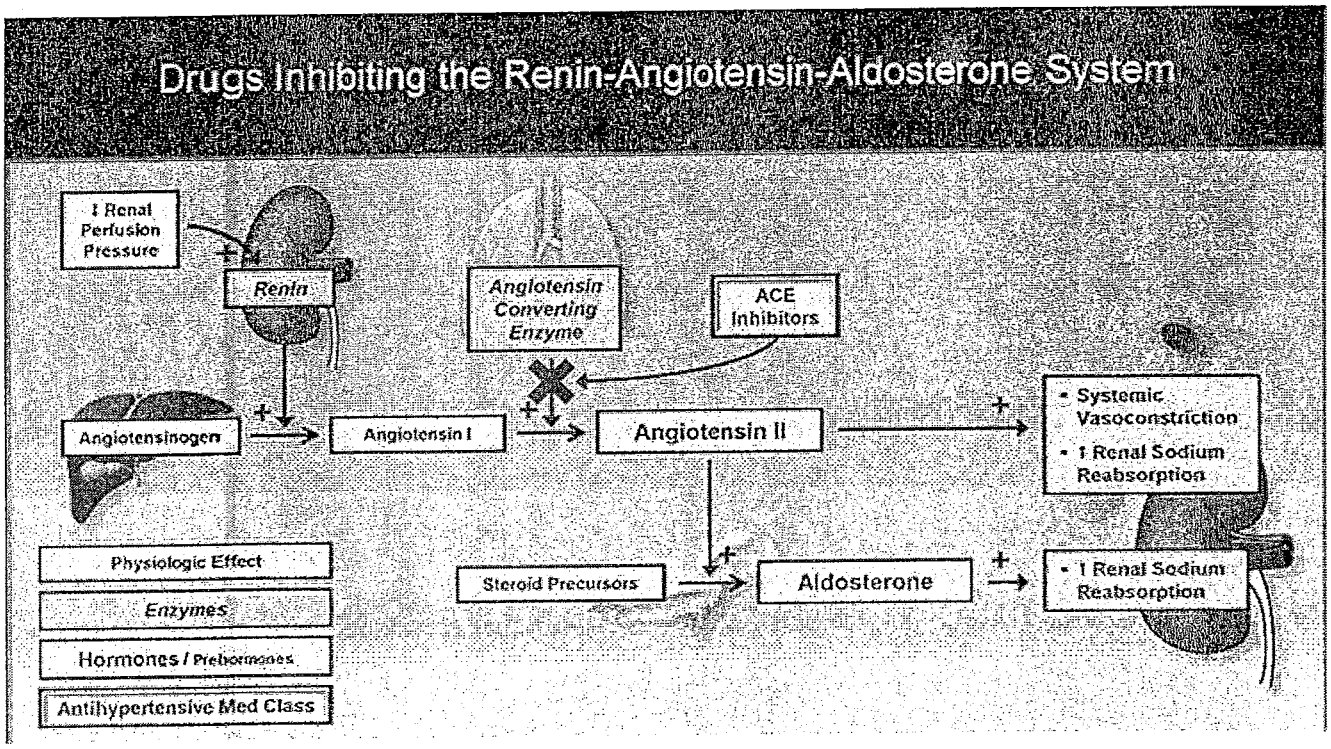
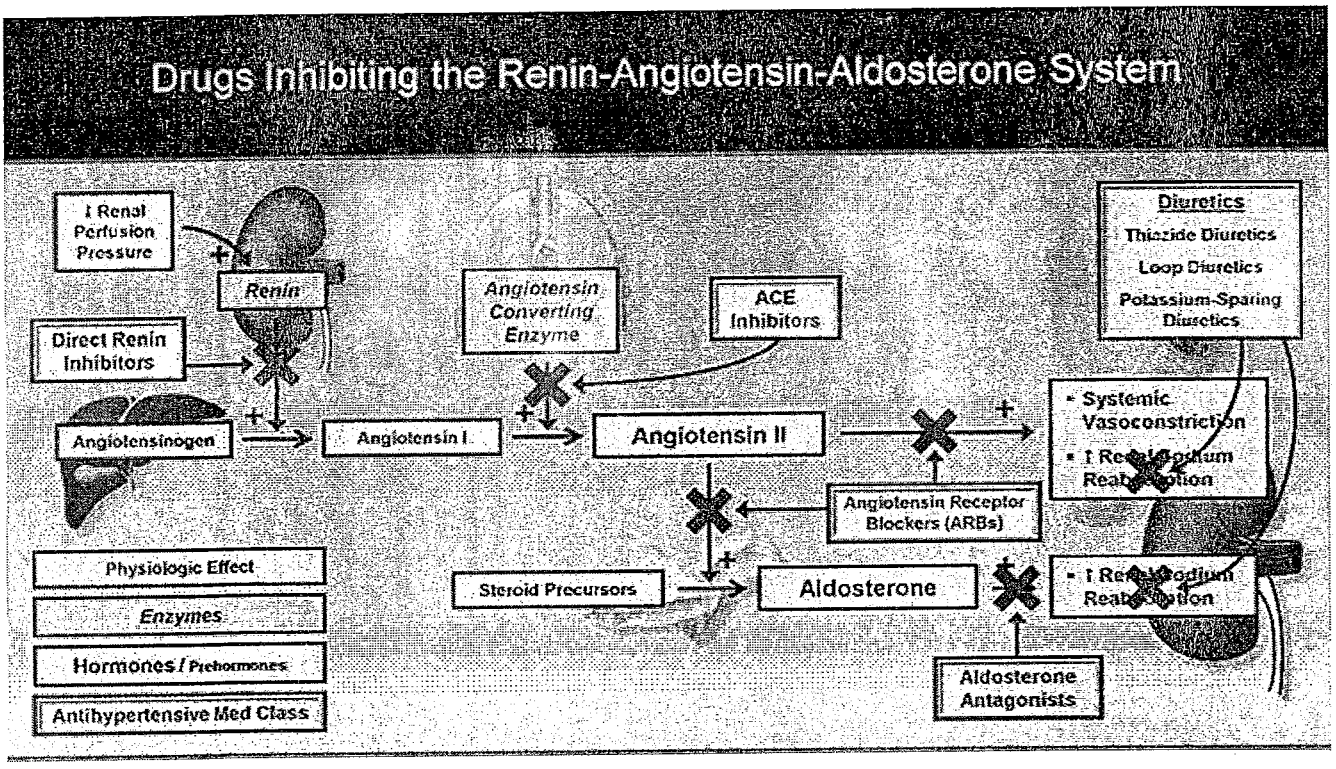


Figure 17.4
Response of the autonomic nervous system and the renin–angiotensin–aldosterone system to a decrease in blood pressure.




Drugs Inhibiting the Renin-Angiotensin-Aldosterone System
↓ Renal Perfusion Pressure
Renin
Angiotensin Converting Enzyme
ACE Inhibitors
Angiotensinogen
Angiotensin I
Angiotensin II
- Systemic Vasoconstriction
- ↑ Renal Sodium Reabsorption
Steroid Precursors
Aldosterone
- ↑ Renal Sodium Reabsorption
Physiologic Effect
Enzymes
Hormones / Prehormones
Antihypertensive Med Class


Drugs Inhibiting the Renin-Angiotensin-Aldosterone System
↓ Renal Perfusion Pressure
Renin
Direct Renin Inhibitors
Angiotensin Converting Enzyme
ACE Inhibitors
Diuretics
Thiazide Diuretics
Loop Diuretics
Potassium-Sparing Diuretics
Angiotensinogen
Angiotensin I
Angiotensin II
- Systemic Vasoconstriction
- ↑ Renal Sodium Reabsorption
Angiotensin Receptor Blockers (ARBs)
Steroid Precursors
Aldosterone
- ↑ Renal Sodium Reabsorption
Aldosterone Antagonists
Physiologic Effect
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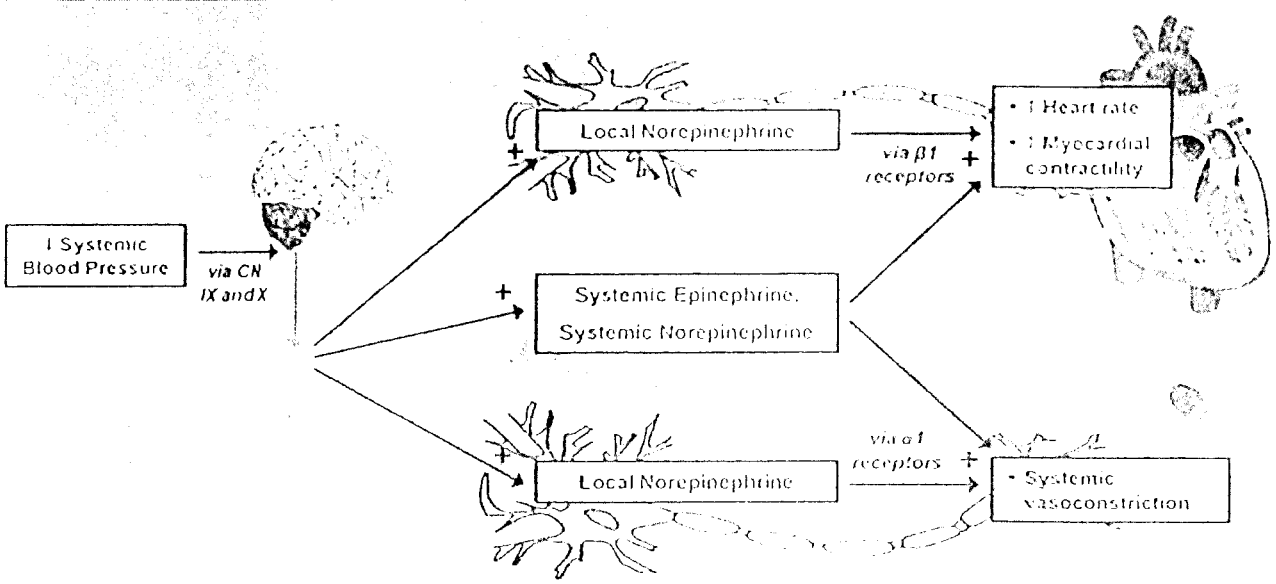
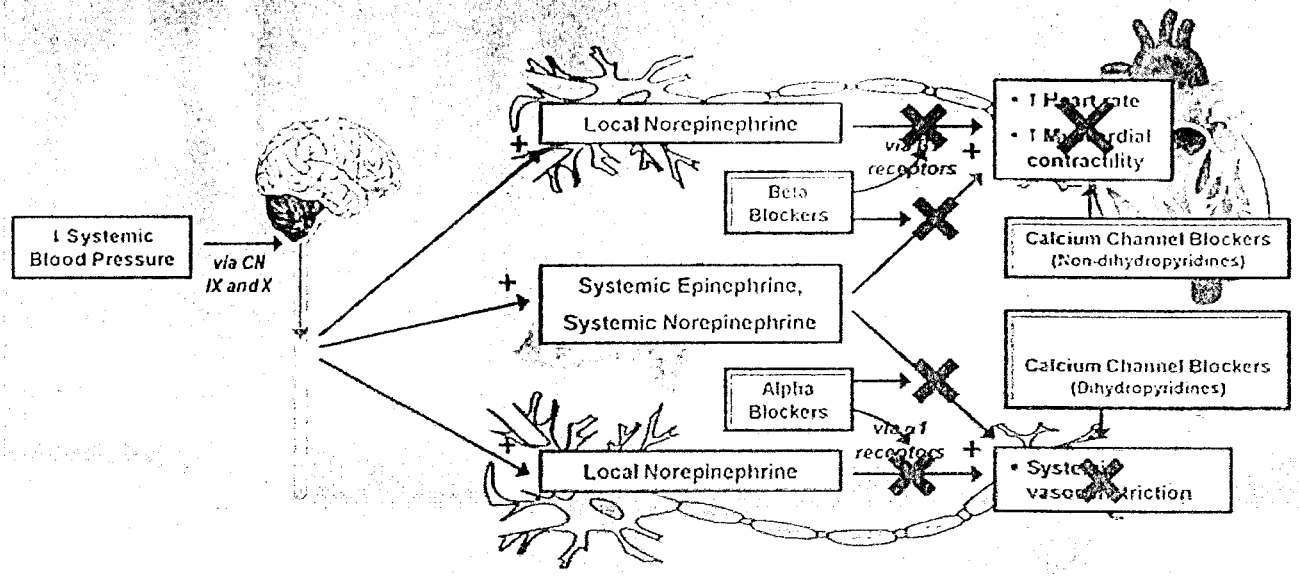
Antihypertensive Med Class

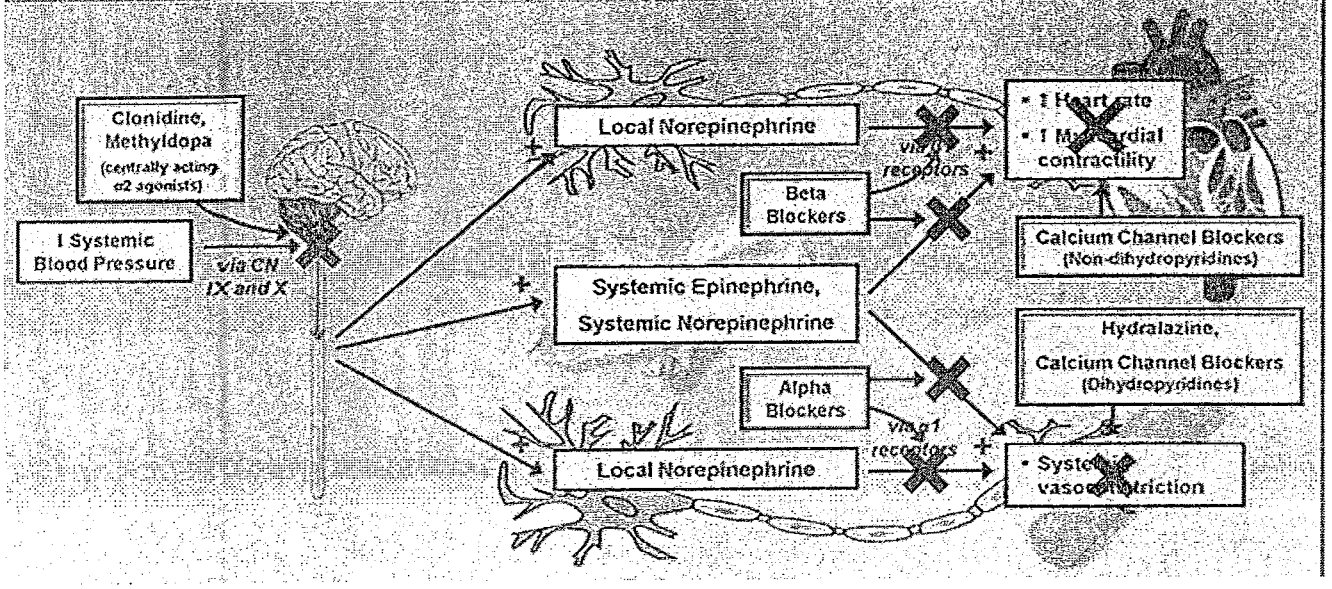
Drugs Inhibiting the Sympathetic Nervous System



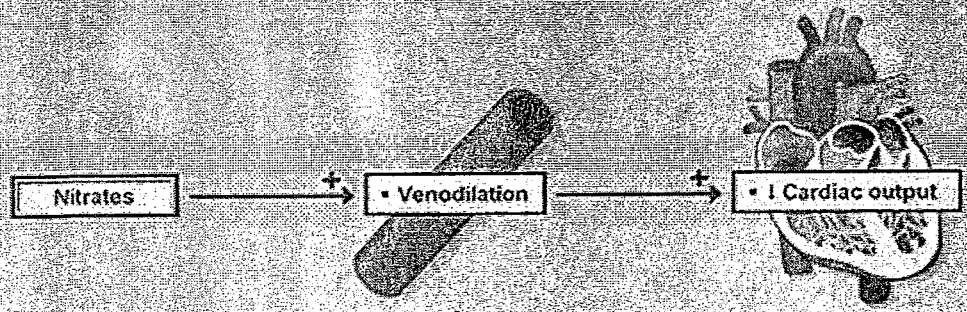
Drugs Inhibiting the Sympathetic Nervous System



Drugs Inhibiting the Sympathetic Nervous System



One Final Drug Mechanism...



Treatment of Hypertension

Table 1. Classification and management of blood pressure for adults*

BP Classification	SBP* mmHg	DBP* mmHg	Lifestyle Modification	Initial Drug Therapy: Without Compelling Indication	Initial Drug Therapy: With Compelling Indications (See Table 8)
Normal	<120	and <80	Encourage		
Prehypertension	120–139	or 80–89	Yes	No antihypertensive drug indicated.	Drug(s) for compelling indications.†
Stage 1 Hypertension	140–159	or 90–99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.	Drug(s) for the compelling indications.† Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
Stage 2 Hypertension	≥160	or ≥100	Yes	Two-drug combination for most‡ (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).	

DBP, diastolic blood pressure; SBP, systolic blood pressure.

Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker.

* Treatment determined by highest BP category.

† Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

‡ Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mmHg.

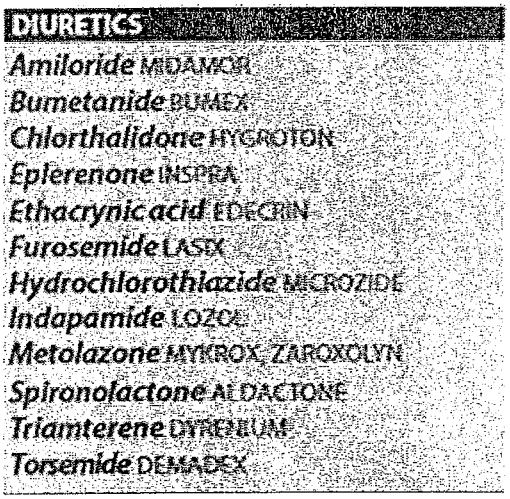
Drugs used for Hypertension

- Diuretics
- β-adrenergic receptor antagonists
- ACE inhibitors
- Angiotension II antagonists
- Ca^{2+} channel blockers
- α_1-adrenergic receptor antagonists
- Centrally acting drugs: α_2-adrenergic receptor agonists

Diuretics

- Decreasing blood volume, which ultimately leads to decreased blood pressure.
- Low-dose diuretic therapy is safe, inexpensive, and effective in preventing stroke, myocardial infarction, and heart failure

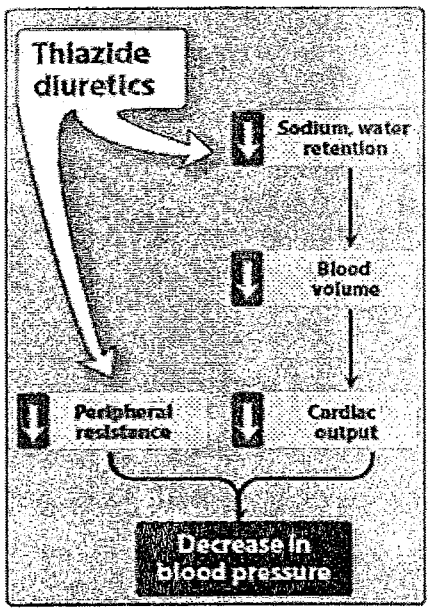
1) **Thiazide diuretic**
2) **Loop diuretic**
3) **Potassium Sparing Diuretics**



Diuretics

1) Thiazide diuretics

- *lower blood* pressure by increasing sodium and water excretion. This causes a decrease in extracellular volume, resulting in a decrease ir cardiac output and renal blood flow.
- With long-term treatment, plasma volume approaches a normal value, but a hypotensive effect persists that is related to a decrease in peripheral resistance.
- With the exception of *metolazone*, thiazide diuretics are not effective in patients with inadequate kidney function (estimated glomerular filtration rate less than 30 mL/min/m2). Loop diuretics may be required in these patients.



Diuretics

1) Thiazide diuretics

- Hydrochlorothiazide, and Thiazide-like (Metolazone, Chlorthalidone, Indapamide).
- Can be used as initial drug therapy for hypertension unless there are compelling reasons to choose another agent.
- Thiazides are useful in combination therapy with a variety of other antihypertensive agents, including β-blockers, ACE inhibitors, ARBs, and potassium-sparing diuretics.
- Can induce hypokalemia, hyperuricemia, hypercalcemia and, to a lesser extent, hyperglycemia and hyperlipidemia in some patients.
- Routine serum electrolyte monitoring should be done for all patients receiving diuretics.

Diuretics

2) Loop diuretics

- *Furosemide, torsemide, bumetanide, and ethacrynic acid.*
- *act promptly by blocking sodium and chloride reabsorption* in the kidneys, even in patients with poor renal function or those who have not responded to thiazide diuretics.
- Can induce hypokalemia, hyperuricemia, hypocalcemia

3) Potassium Sparing Diuretics

- *Amiloride, triamterene, spironolactone, eplerenone*
- Potassium-sparing diuretics are sometimes used in combination with loop diuretics and thiazides to reduce the amount of potassium loss induced by these diuretics.

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β-adrenergic receptor antagonists

- Binds to Beta adrenoreceptors and competitively competes with norepinephrine and epinephrine at these sites
- Some are partial agonists; partially activating the beta receptor while blocking norepinephrine

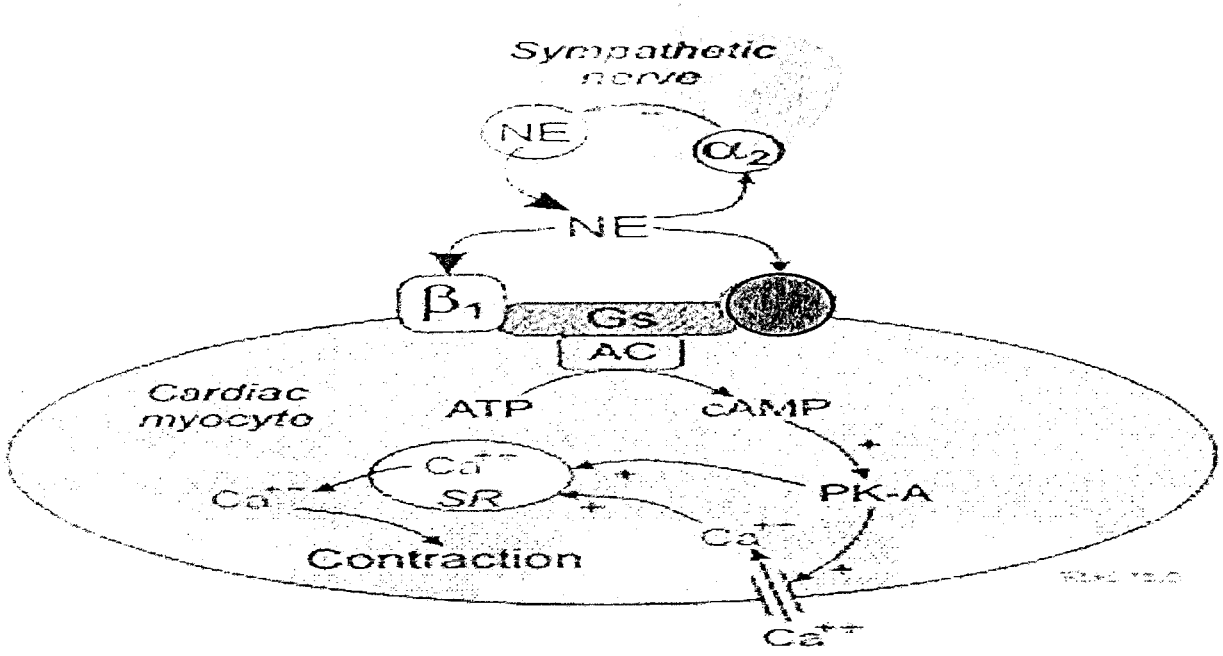
- First generation are non selective meaning blocks both beta 1 and beta 2 adrenoreceptors
- Second generation are relatively selective for beta 1 adrenoreceptors or cardioselective
- Third generation possess vasodilator activity by blockade of vascular alpha adrenoreceptors

β-BLOCKERS

Acebutolol SECTRAL
Atenolol TENORMIN
Betaxolol KERLONE
Bisoprolol ZEBETA
Carvedilol COREG, COREG CR
Esmolol BREVIBLOC
Labetalol TRANDATE
Metoprolol LOPRESSOR, TOPROL-XL
Nadolol CORGARD
Nebivolol BYSTOLIC
Penbutolol LEVATOL
Pindolol VISKEN
Propranolol INDERAL LA, INNOPRAN XL
Timolol BLOCADREN

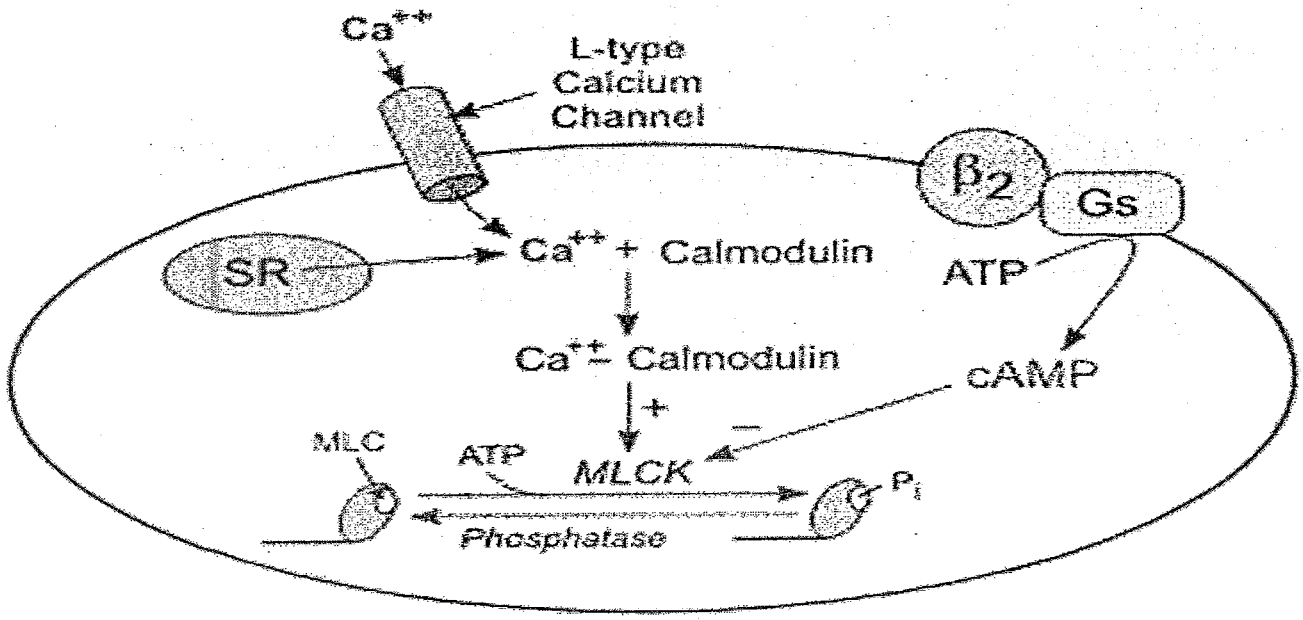
- Beta 1 receptors in the heart upon stimulation increase HR, contractility, AV conduction
- Beta 2 receptors, some in heart but mostly in bronchial muscle and peripheral vascular muscle that result in relaxation
- Beta 3 receptors in heart and adipose tissue, mediate thermogenesis

Sympathetic nerve terminal to cardiac myocyte



Abbreviations: NE, norepinephrine; Gs, G-stimulatory protein; AC, adenylyl cyclase; PK-A, cAMP-dependent protein kinase; SR, sarcoplasmic reticulum

Sympathetic nerve terminal to vascular smooth muscle



Abbreviations: SR, sarcoplasmic reticulum; Gq, Gs-protein; MLC, myosin light chain; MLCK, myosin light chain kinase; Pi, myosin phosphorylation

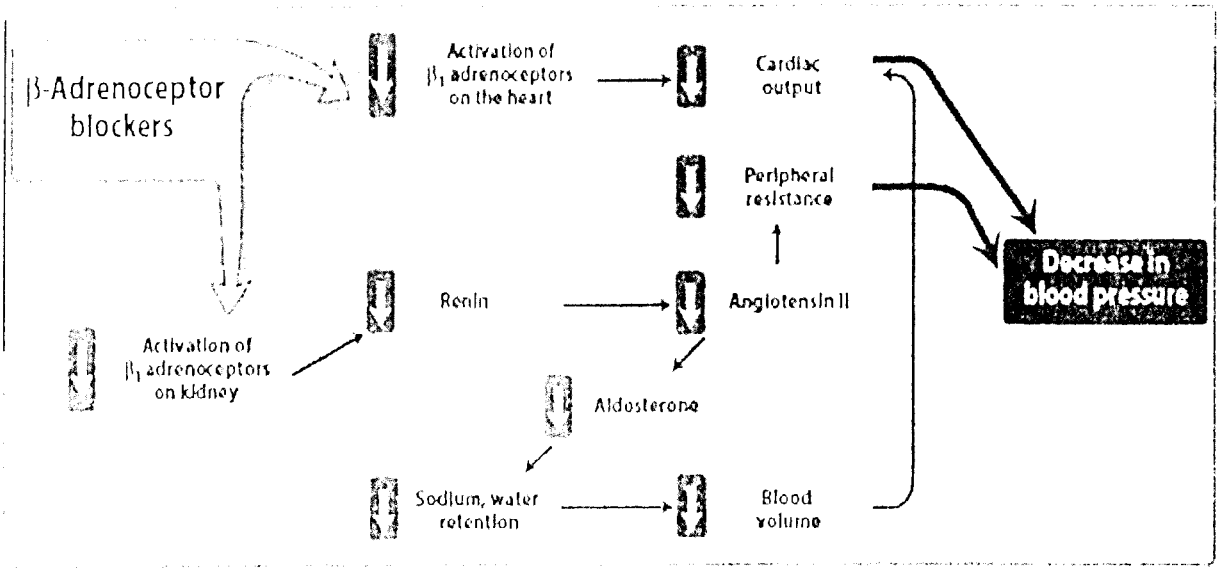
β-adrenergic receptor antagonists

- The β-blockers reduce blood pressure by:

  - decreasing cardiac output

  - inhibiting the release of renin from the kidneys (mediated by β1 receptors), thus decreasing the formation of angiotensin II and the secretion of aldosterone.

- Non selective blockers β-blocker acts at both β1 and β2 receptors such as *propranolol* .
- Selective blockers of β1 receptors, such as *metoprolol and nebivolol are among the most commonly prescribed* β-blockers.



Therapeutic use

- The primary therapeutic benefits of β-blockers are seen in hypertensive patients with concomitant heart disease, myocardial infarction, angina pectoris, and chronic heart failure.
- Conditions that discourage the use of β-blockers include reversible bronchospastic disease such as asthma, and severe peripheral vascular disease