Anti-hypertensive drugs
Definition of Hypertension


Hypertension, in people aged 18 years or older, is a medical condition in which the systolic or diastolic blood pressure is higher than the physiological values, monitored over a 6 months period.

- The European Society of Hypertension Guidelines and British Hypertension Society did not adopt JNC8 without comments, but they both defined the pressure values for physiological and pathological classification of the blood pressure.

<table>
<thead>
<tr>
<th>Blood pressure classification for adults</th>
<th>Systolic Blood Pressure</th>
<th>Diastolic Blood Pressure</th>
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<tbody>
<tr>
<td>Normal</td>
<td>&lt; 120 mm Hg</td>
<td>&lt; 80 mm Hg</td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>120 – 139 mm Hg</td>
<td>80 – 89 mm Hg</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>140 – 159 mm Hg</td>
<td>90 – 99 mm Hg</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>&gt; 160 mm Hg</td>
<td>≥ 100 mm Hg</td>
</tr>
</tbody>
</table>
Types of Hypertension

- Hypertension can be classified into:

1) **Primary (Essential) Hypertension.** Numerous common genetic variants with small effects on blood pressure have been identified. Usually, primary hypertension results from a complex interaction of genes and environmental factors.

2) **Secondary (Symptomatic) Hypertension.** Results from another disease (Kidney disease, endocrine conditions, obesity, sleep apnea, pregnancy, coarctation of the aorta, excessive eating of liquorice, certain prescription medicines, herbal remedies, and stimulants such as cocaine and methamphetamine.

A review published in 2018 found that any alcohol increased blood pressure in males while over one or two drinks increased the risk in females (Roerecke M, et al. “Sex-Specific Associations Between Alcohol Consumption and Incidence of Hypertension: A Systematic Review and Meta-Analysis of Cohort Studies. J Am Heart Assoc. 2018;7(13). pii: e008202).
The pathophysiology of essential hypertension

- **Genetic influences**
  - Defects in renal sodium haemostasis
    - Inadequate sodium excretion
      - Sodium and water retention
        - ↑ Plasma and ECF volume
          - ↑ Cardiac output (autoregulation)
            - Hypertension

- **Environmental factors**
  - Functional, vasoconstriction
    - ↑ Natriuretic hormone
      - ↑ Vascular reactivity
        - ↑ Total peripheral resistance
          - ↑ Vascular wall thickness

- Defects in vascular smooth muscle growth and structure
Physiological regulation of blood pressure
Targets for anti-hypertensive drugs

Alpha₂ agonists
Decrease sympathetic impulses from the CNS to the heart and arterioles, causing vasodilation

Alpha₁ blockers
Inhibit sympathetic activation in arterioles, causing vasodilation

Direct vasodilators
Act on the smooth muscle of arterioles, causing vasodilation

Calcium channel blockers
Block calcium ion channels in arterial smooth muscle, causing vasodilation

Angiotensin receptor blockers
Prevent angiotensin II from reaching its receptors, causing vasodilation

ACE inhibitors
Block formation of angiotensin II, causing vasodilation and block aldosterone secretion, decreasing fluid volume

Beta blockers
Decrease the heart rate and myocardial contractility, reducing cardiac output
Why treat hypertension?

To decrease:

a) Cerebrovascular accidents (35-40%)

b) Coronary events (20-25%)

c) Heart failure (50%)

d) Progression of renal disease

e) Progression to severe hypertension
Classes of anti-hypertensive drugs

a) Diuretics

b) β-blockers

a) Autacoids

b) ACE inhibitors

c) Angiotensin type 1 receptor antagonists

d) Ca++ channel blockers

e) α1-antagonists

f) Other
Diuretics

Diuretic drugs are classified according to their predominant site of action:

1) The loop diuretics (furosemide, bumetanide, and torsemide) act from the lumen to inhibit the Na-K-2Cl cotransporter along the thick short descending limbs of the loop of Henle and collecting ducts. As organic anions, they bind within the translocation pocket on the transport protein by interacting with the chloride binding site. Because they are larger than chloride, they are not transported through the pocket, and thereby inhibit the transporter.

2) Thiazides and thiazide-like drugs are also organic anions that act in much the same manner, but bind the thiazide-sensitive NaCl cotransporter along the distal convoluted tubule. This mechanism of action accounts for a key aspect of loop and distal convoluted tubule diuretic action; these drugs both exert their effect from the luminal side of the tubule.

3) K⁺-sparing diuretics include drugs that block apical Na⁺ channels (amiloride and triamterene) and those that antagonize mineralocorticoid receptors (spironolactone and eplerenone). The mineralocorticoid blockers and perhaps ethacrynic acid, a more toxic loop diuretic, act within cells and do not require secretion into the tubule lumen.
Loop Diuretics

Loop diuretics have a higher capacity for diuresis compared to other diuretics. Their mechanism of action is based on:

1) Inhibition of Na\(^+\) and Cl\(^-\) reabsorption at the level of the short descending limbs of the loop of Henle and collecting ducts.

2) Increase of the fractional excretion of Ca\(^{++}\) by up to 30% by decreasing the lumen-positive transepithelial potential that promotes paracellular Ca\(^{++}\) reabsorption from the lumen.

3) Increase fractional Mg\(^{++}\) excretion by more than 60%, also by diminishing voltage-dependent paracellular transport.
## Loop Diuretics: an overview

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<tr>
<th>Drug</th>
<th>Indications</th>
<th>Possible Side effects</th>
<th>Potential Interaction</th>
<th>Precautions and Contraindications</th>
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<tr>
<td>Furosemide</td>
<td>• Peripheral edema</td>
<td>• Hypokalemia</td>
<td>• ACE inhibitors</td>
<td><strong>Precautions:</strong>&lt;br&gt;- DM / SLE&lt;br&gt;- Acute MI / arrhythmias&lt;br&gt;- Prostatic hyperplasia/ urinary stricture&lt;br&gt;- Elderly patients**&lt;br&gt;<strong>Contraindications:</strong>&lt;br&gt;- Hypersensitivity to the drug&lt;br&gt;- Hypersensitivity to sulfonamides&lt;br&gt;- Anuria&lt;br&gt;- Hepatic coma</td>
</tr>
<tr>
<td></td>
<td>• Acute pulmonary edema</td>
<td>• Hypochloremia</td>
<td>• Allopurinol</td>
<td></td>
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<tr>
<td></td>
<td>• Hypertension</td>
<td>• Hyperuricemia</td>
<td>• Beta 2-agonists</td>
<td></td>
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<tr>
<td></td>
<td>• Hypercalcemia</td>
<td>• Metabolic alkalosis</td>
<td>• Corticosteroids</td>
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<tr>
<td></td>
<td></td>
<td>• Hyperglycemia</td>
<td>• Ethanervic acid</td>
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<td></td>
<td></td>
<td></td>
<td>• Lithium</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• MAO inhibitors</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Methylphenidate</td>
<td></td>
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<td></td>
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<td></td>
<td>• Phenytoin</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>• Probenecid</td>
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</table>

**ACE inhibitors:** Angiotensin-converting enzyme inhibitors; **DM:** Diabetes mellitus; **MAO inhibitors:** Monoamine oxidase inhibitors; **MI:** Myocardial infarction; **SLE:** Systemic lupus erythematosus
Furosemide

- Furosemide is a sulfonamide derivative of aminobenzoic acid.
- Furosemide is available in oral and injectable forms, with approximately 65% absorption of the oral form. Diuresis begins within 5 minutes of intravenous administration with a duration of 2 hours, and it begins approximately 30 minutes after oral or intramuscular administration and lasts from 6 to 8 hours. Furosemide is highly protein bound, metabolized by the liver, and excreted in the urine and feces. With normal renal function, it has a half-life of 30 to 70 minutes, but this increases to approximately 9 hours in patients with end-stage renal disease.
- Loop diuretics are the drugs of choice for the treatment of acute pulmonary edema. In this condition, furosemide is usually administered parenterally, producing a rapid reduction in pulmonary congestion. At the level of the whole body, loop diuretics reduce the extracellular fluid volume and reduce blood pressure with a greater magnitude compared with thiazides. Furosemide also increases venous capacitance, which reduces left ventricular filling pressure. This effect seems to be mediated by prostaglandins and occurs before diuresis, and is especially useful with intravenous furosemide to treat acute pulmonary edema.
- Toxicity from loop diuretics is usually the result of plasma electrolyte disturbances such as hyponatremia and hypokalemia and extracellular volume depletion. The magnitude of these effects can be greater than the effects produced by thiazides because of the more prominent natriuresis produced by loop diuretics. Furosemide may also cause photosensitivity dermatitis.
Thiazide and thiazide-like diuretics

- Thiazide and thiazide-like diuretics inhibit Na\(^+\)Cl\(^-\) cotransport.

Their mechanism of action is based on:

1) increase in the excretion of NaCl and reduction of extracellular fluid volume. This event result in a reduction in the Na\(^+\) and Cl\(^-\) reabsorption by the distal convoluted tubule and an increase in the amounts of Na\(^+\) and Cl\(^-\) delivered to the collecting duct. Some of the Na\(^+\) that is delivered to the collecting duct is excreted with an equivalent amount of water, producing natriuresis and diuresis, and some is reabsorbed in the cortical collecting duct as it is exchanged for K\(^+\) or H\(^+\).

2) increase the reabsorption of filtered Ca\(^{++}\). This action distinguishes these compounds from loop diuretics, which promote Ca\(^{++}\) excretion.

3) Mg\(^{++}\) initial reabsorption is also initially increased by thiazides, but subsequent loss.
<table>
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<tr>
<th>Drug</th>
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<th>Possible Side effects</th>
<th>Some Potential Interactions</th>
<th>Precautions and Contraindications</th>
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</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide</td>
<td>• Hypertension&lt;br&gt;• Hypercalcemia&lt;br&gt;• Edema&lt;br&gt;<strong>Additional Chlorthalidone</strong>&lt;br&gt;• Renal tubular acidosis</td>
<td>• Hypokalemia&lt;br&gt;• Hyponatremia&lt;br&gt;• Hyperuricemia&lt;br&gt;• Metabolic alkalosis&lt;br&gt;• Hyperglycemia&lt;br&gt;• Photosensitivity</td>
<td>• Lithium&lt;br&gt;• NSAIDs&lt;br&gt;• Hypoglycemic agents&lt;br&gt;• Corticosteroids</td>
<td><strong>Precautions:</strong>&lt;br&gt;• Electrolyte abnormalities&lt;br&gt;• Dehydration&lt;br&gt;• DM/ SLE&lt;br&gt;• Elderly patients&lt;br&gt;• Pregnancy/ lactation&lt;br&gt;<strong>Contraindications:</strong>&lt;br&gt;• Hypersensitivity to drug and/or its components&lt;br&gt;• Anuria</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td></td>
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<td></td>
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<tr>
<td>Indapamide</td>
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</tbody>
</table>
Hydrochlorothiazide is the most commonly prescribed thiazide diuretic.

Hydrochlorothiazide is well absorbed (65% to 75%) following oral administration. Absorption of hydrochlorothiazide is reduced in patients with congestive heart failure. Peak plasma concentrations are observed within 1 to 5 hours of dosing. Binding to serum proteins has been reported to be approximately 40% to 68%. The plasma elimination half-life has been reported to be 6 to 15 hours. Hydrochlorothiazide is eliminated primarily by renal pathways.

The JNC8 and the World Health Organization recommend thiazide diuretics as a first-line treatment for Stage 1 hypertension because of their demonstrated efficacy and low cost.

Thiazide diuretics are generally safe and effective drugs. Toxicity usually is a result of plasma electrolyte disturbances, which can result in extracellular volume depletion, hyponatremia, and hypokalemia. Most prevalent among these is hypokalemia, which results from the combined effects of volume depletion–induced aldosterone release and increased delivery of Na⁺ and Cl⁻ to the collecting duct. Hyperglycemia can occur in nondiabetic patients treated with thiazide diuretics, and glucose control can be destabilized in diabetic patients.
Hydrochlorothiazide combinations with other drugs

- $\text{K}^+$-sparing diuretics.
- Another antihypertensive drug.
K⁺ -sparing diuretics

- K⁺ -sparing agents can be divided into those that antagonize aldosterone (spironolactone and eplerenone) and those independent of aldosterone (amiloride and triamterene).

All of the drugs in this class:

1) inhibit Na⁺ absorption in the distal tubule and the collecting duct.

2) with the reduction in Na⁺/K⁺ ATPase, K⁺ secretion is reduced. This effect can lead to hyperkalemia and limit their use in patients with reduced renal function and in some with heart failure.

3) reduce the excretion of Ca²⁺ and Mg²⁺.
# K+-sparing diuretics: an overview

<table>
<thead>
<tr>
<th><strong>Potassium-sparing diuretics</strong></th>
<th>Spironolactone and eplerenone; Triamterene, and Amiloride.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td>Spironolactone and eplerenone are competitive aldosterone receptor antagonists in cortical collecting tubule. Triamterene and amiloride act at the same part of the tubule by blocking Na⁺ channels in the cortical collecting tubule.</td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
<td>Hyperaldosteronism, K⁺ depletion, HF, hepatic ascites (spironolactone), nephrogenic DI (amiloride), antiandrogen.</td>
</tr>
<tr>
<td><strong>ADVERSE EFFECTS</strong></td>
<td>Hyperkalemia (can lead to arrhythmias), endocrine effects with spironolactone (eg, gynecomastia, antiandrogen effects).</td>
</tr>
</tbody>
</table>

Abbreviations: HF: heart failure; nephrogenic DI: nephrogenic diabetes insipidus
Spironolactone

- Spironolactone is a 17-spirolactone steroid that is structurally similar to aldosterone and functions as an aldosterone antagonist.

- Spironolactone is administered orally and is rapidly absorbed. However, the onset of action takes 2 to 4 days and full clinical efficacy is not seen for several weeks. Spironolactone is metabolized by the liver and has two active metabolites, canrenone and canrenoate. Canrenone is prescribed as a K+-sparing diuretic in Europe.

- K+ -sparing diuretics are most often used to prevent hypokalemia caused by thiazide and loop diuretics. Spironolactone is also sometimes used in the treatment of hyperaldosteronism. Spironolactone also has been found to be useful in the treatment of congestive heart failure.

- The primary toxic effect of K+ -sparing diuretics is hyperkalemia. This effect is most common when these drugs are given without another diuretic or concomitantly with other inhibitors of K+ excretion, such as angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists. Spironolactone, because of its steroid structure, can also produce gynecomastia and/or decreased libido in men. Menstrual irregularities have been reported for women.
β-blockers

Their effects have been attributed to the following actions:
1) blockade of cardiac β1 receptors inhibits the release of cAMP-dependent protein kinase that can not increase the Ca²⁺ reuptake, the number of opened Ca²⁺ channels and the velocity of contraction.
2) blockade of β1 receptors in the juxtaglomerular complex reduces renin secretion, and consequently circulating angiotensin II.

Two of the major guide-line committees (JNC8 and NICE UK) have dropped β-blockers as first-line therapy in the treatment of hypertension. Moreover, a recent meta-analyses have concluded that β-blockers are inappropriate first-line agents in the treatment of hypertension (Wiysonge CS et al. 2017. "Beta-blockers for hypertension". The Cochrane Database of Systematic Reviews. 1: CD002003).
## Selected studies on β-blockers in hypertension.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Srivastava et al&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Double-blind prospective trial</td>
<td>20</td>
<td>Treatment benefits versus placebo did not reach statistical significance</td>
</tr>
<tr>
<td>Prichard and Gillam&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Prospective trial</td>
<td>109</td>
<td>92 of the patients in propranolol group achieved a supine, or standing BP of 100 mm Hg or less</td>
</tr>
<tr>
<td>MRC Working Party&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Randomized, placebo-controlled, single-blind trial in elderly</td>
<td>4,396 (aged 65-74 years)</td>
<td>Atenolol-treated patients showed no significant reduction in stroke, coronary events, and all CV events</td>
</tr>
<tr>
<td>Gupta et al (ASCOT)&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Randomized, comparator trial</td>
<td>19,257</td>
<td>Patients assigned to atenolol +/- thiazide developed more NOD</td>
</tr>
<tr>
<td>Lindholm et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Meta-analysis of 7 randomized trials</td>
<td>27,433</td>
<td>β-blockers raised the risk of stroke</td>
</tr>
<tr>
<td>Law et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Meta-analysis of 108 randomized trials</td>
<td>464,000</td>
<td>No significant difference among major antihypertensives</td>
</tr>
<tr>
<td>Fretheim et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Meta-analysis of 25 randomized trials</td>
<td>164,671</td>
<td>β-blockers not superior to other antihypertensives</td>
</tr>
<tr>
<td>Mahmud and Feely&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Comparator trial of atenolol and nebivolol</td>
<td>40</td>
<td>Nebivolol, but not atenolol, reduced aortic stiffness</td>
</tr>
<tr>
<td>Bangalore et al&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Comparative meta-analysis of 22 clinical trials</td>
<td>68,222</td>
<td>β-blockers-induced decreased HR increased risk of cardio-vascular events and death</td>
</tr>
<tr>
<td>Phillips et al (GEMINI)&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Comparative trial of carvedilol and metoprolol</td>
<td>1,235</td>
<td>Carvedilol is better in hypertensive patients with diabetes</td>
</tr>
<tr>
<td>Lewin et al&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Nebivolol monotherapy in stage II hypertension</td>
<td>290</td>
<td>Nebivolol was significantly effective even in patients with BMI ≥ 30 Kg/m²</td>
</tr>
<tr>
<td>Zeltner et al&lt;sup&gt;69&lt;/sup&gt;</td>
<td>Comparative trial of ramipril vs metoprolol in PCKD</td>
<td>46</td>
<td>No significant difference in proteinuria, renal function, and LVMII in 3 years follow-up</td>
</tr>
<tr>
<td>Caglar and Dincer (PROBE)&lt;sup&gt;72&lt;/sup&gt;</td>
<td>Comparative trial of nebivolol and ramipril in hypertensive patients with LV hypertrophy</td>
<td>106</td>
<td>Nebivolol significantly reduced LVMII, and at a lower dose</td>
</tr>
<tr>
<td>Collier et al (ASCOT-BPLA)&lt;sup&gt;80&lt;/sup&gt;</td>
<td>Comparative trial of atenolol and amlodipine in younger and older hypertensive patients</td>
<td>19,257</td>
<td>Amlodipine reduced relative risk of CV events more effectively than atenolol in both older and younger patients</td>
</tr>
<tr>
<td>Pareek et al&lt;sup&gt;92&lt;/sup&gt;</td>
<td>Comparative trial of metoprolol XL/amlodipine combination vs losartan/amlodipine combination</td>
<td>148</td>
<td>Both combinations were equally effective in lowering SBP and DBP</td>
</tr>
</tbody>
</table>

- **CV** - cardiovascular
- **NOD** - newonset diabetes
- **HR** - heart rate
- **BMI** - body mass index
- **LVMII** - left ventricular mass index
- **PCKD** - polycystic kidney disease
- **SBP** - systolic blood pressure
- **DBP** - diastolic blood pressure
β–blockers used in hypertension with comorbidities

The β-blockers are still preferred in hypertensive patients who have suffered from myocardial infarction, or other forms of ischemic heart diseases, and heart failure due to systolic dysfunction, **but not in hypertensive patients without comorbidities**. β-blockers are usually avoided in patients suffering from bronchial asthma, or with airway hyper-reactivity.

**β receptor antagonists**

- **Non-selective (First Generation)**
  - Nadolol
  - Penbutolol
  - Pindolol
  - Propanolol
  - Timolol
  - Sotalol
  - Levobunolol
  - Metipranolol

- **β₁-selective (2nd Generation)**
  - Acebutolol
  - Atenolol
  - Bisoprolol
  - Esmolol
  - Metoprolol

- **Non-selective (3rd Generation)**
  - Carteolol
  - Carvedilol
  - Bucindolol
  - Labetalol

- **β₁-selective (3rd Generation)**
  - Betaxolol
  - Celiprolol
  - Nebivolol
Adverse effects of β–blockers

Adverse drug reactions associated with the use of β–blockers include:

- nausea,
- diarrhea,
- bronchospasm,
- dyspnea,
- cold extremities,
- exacerbation of Raynaud's syndrome,
- bradycardia,
- hypotension,
- heart failure,
- heart block,
- fatigue,
- dizziness,
- alopecia,
- abnormal vision,
- hallucinations,
- insomnia,
- nightmares,
- sexual dysfunction/erectile dysfunction
- alteration of glucose and lipid metabolism.
β-Blockers may interact with a large number of commonly prescribed drugs, including:

- anti-hypertensive and antianginal drugs,
- inotropic agents,
- anti-arrhythmics,
- NSAIDs,
- psychotropic drugs,
- anti-ulcer medications,
- anaesthetics,
- HMG-CoA reductase inhibitors,
- warfarin,
- oral hypoglycaemics and rifampicin.
Autacoids, also known as local hormones, are a group of endogenous substances produced by a wide variety of cells. Autacoids have several biological action and act near the site of synthesis.

Autacoids can be classified basing on their chemical structure into:
Synthesis of Bradykinin

Hageman factor
Trypsin
Kallikrein

Plasma prekallikrein → Plasma kallikrein

HMW kininogen → Bradykinin

Aminopeptidases

LMW kininogen → Kallidin

Tissue kallikreins

Kininases I and II

Inactive fragments

Chemical structure of Bradykinin.
The role of bradykinin in hypertension has been established for more than three decades, with the observations that urinary kallikrein excretion is significantly reduced in hypertensive patients and hypertensive rats.

The pharmacologic action of bradykinin in the regulation of systemic blood pressure involves:
1) vasodilatation in most areas of the circulation,
2) reduction of total peripheral vascular resistance,
3) regulation of Na\(^+\) excretion from the kidney.

When bradykinin is injected into the renal artery, it causes **diuresis and natriuresis** by increasing renal blood flow. These actions of bradykinin have been attributed to prostaglandin release in the renal circulation. This led to the suggestion that reduced urinary kallikrein excretion might result from a defect in kinin generation in hypertensive situations.
Synthesis angiotensin and catabolism bradykinin

Kininase II (ACE) inhibitors are currently used in the treatment of both clinical and experimental hypertension.

Kininase II inhibitors could lower blood pressure by inhibiting the biodegradation of bradikinin and blocking the formation of angiotensin II.
ACE inhibitors

ACE inhibitors work:

1) causing relaxation of blood vessels as well as a decrease in blood volume, which leads to lower blood pressure and decreased oxygen demand from the heart.

2) increasing blood flow, which helps to decrease the amount of work that heart has to do and can help to protect the kidney from the effects of hypertension and diabetes.
Angiotensin II: Effects

Change in Peripheral Resistance:
- Direct Vasoconstriction
- Sympathetic Discharge
- Adrenal Medullary Catecholamine Release
- Noradrenergic Enhancement
  (1) decreased reuptake
  (2) increased release
  (3) increased vascular responsiveness

Change in Renal Function:
- Sodium Reabsorption (direct and aldosterone mediated)
- Direct renal vasoconstriction
- Noradrenergic transmission
- Renal sympathetic tone

Structural Changes Remodeling:
- Proto-oncogene expression
- Growth Factors
- Afterload
- Wall Tension

Rapid Pressor Response
Slow Pressor Response
Vascular and Cardiac Hypertrophy & Remodeling
Mechanisms of ACE inhibitors-mediated anti-hypertensive effects
Chemical classification of ACE inhibitors

- Peptide structure:
  1) Direct-acting ACE inhibitors (Captopril, Lisinopril, Enalaprilat)
  2) Pro-drugs (de-esterified in the liver to active diacid forms).

- Three subgroups:
  1) Sulphydryl- containing (Captopril, Zefnopril, Alacepril, Pivalopril);
  2) Di-carboxyl-containing (Enalapril, Lisinopril, Quinalapril, Ramipril, Perindopril);
  3) Phosphorus-containing (Fosinopril).
## ACE inhibitors: an overview

| **Angiotensin-converting enzyme inhibitors** | Captopril, enalapril, lisinopril, ramipril. |
| **MECHANISM** | Inhibit ACE $\rightarrow$ ↓ AT II $\rightarrow$ ↓ GFR by preventing constriction of efferent arterioles. ↑ renin due to loss of negative feedback. Inhibition of ACE also prevents inactivation of bradykinin, a potent vasodilator. |
| **CLINICAL USE** | Hypertension, HF (↓ mortality), proteinuria, diabetic nephropathy. Prevent unfavorable heart remodeling as a result of chronic hypertension. |
| **ADVERSE EFFECTS** | Cough, Angioedema (due to ↑ bradykinin; contraindicated in Cl esterase inhibitor deficiency), Teratogen (fetal renal malformations), ↑ Creatinine (↓ GFR), Hyperkalemia, and Hypotension. Used with caution in bilateral renal artery stenosis because ACE inhibitors will further ↓ GFR $\rightarrow$ renal failure. |

**Abbreviations:** AT II: angiotensin II; GFR: glomerular filtration rate; HF: heart failure
Captopril is the prototype of the sulfhydryl-containing ACE inhibitors. In vitro studies suggest that the presence of the sulfhydryl group may confer properties other than ACE inhibition to these drugs, such as free-radical scavenging and effects on prostaglandins.

Captopril was the first orally active ACE inhibitor, but it differs from other ACE inhibitors by its short half-life (<2 hours), necessitating multiple administrations per day. Captopril is metabolized in the liver and then excreted by the kidney.

Captopril is most effective in patients with an activated renin-angiotensin system, such as those with accelerated or malignant hypertension, scleroderma, and other forms of renal vasculitis. The antihypertensive response is exacerbated by volume depletion, which can lead to hypotension requiring aggressive intravenous fluid replacement.

The sulfhydryl group increases the frequency of some side effects. The most common side effects of ACE inhibitors are dry cough, skin rash, angioedema, and dysgeusia (distortion of taste). Neutropenia and agranulocytosis may appear after 3 to 12 weeks of therapy, particularly in patients with autoimmune collagen vascular diseases. Another notable side effect is worsening of anemia in dialysis patients.
Enalapril

- Enalapril is a prodrug which when administered orally is hydrolysed to release the active converting enzyme inhibitor enalaprilat.
- Peak plasma enalaprilat concentrations occur 2 to 4 hours after oral enalapril administration. Elimination is biphasic, with an initial phase which reflects renal filtration (elimination half-life 2 to 6 hours) and a subsequent prolonged phase (elimination half-life 36 hours), the latter representing equilibration of drug from tissue distribution sites.
- Enalapril is used to treat hypertension, symptomatic heart failure, and asymptomatic left ventricular dysfunction. It has been proven to protect the function of the kidneys in hypertension, heart failure, and diabetes, and may be used in the absence of hypertension for its kidney protective effects. It is widely used in chronic kidney failure. Furthermore, enalapril is an emerging treatment for psychogenic polydipsia. A double-blind, placebo-controlled trial showed that when used for this purpose, enalapril led to decreased water consumption (determined by urine output and osmality) in 60% of patients.
- The most common side effects of enalapril include increased serum creatinine (20%), dizziness (2–8%), low blood pressure (1–7%), syncope (2%), and dry cough (1–2%). The most serious common adverse event is angioedema (0.68%), which often affects the face and lips, involving the patient's airway. Angioedema can occur at any point during treatment, but is most common after the first few doses. Angioedema and fatality are reportedly higher among black people.
Angiotensin II type 1 receptor antagonists

Liver secretion → Angiotensinogen

Kidney secretion → Renin

ACE-Independent Pathways

ACE-Dependent Pathways

Angiotensin I

Direct Renin Inhibitor

ACE Inhibitors

Angiotensin II

Angiotensin II Type 1 Receptor Blockers

Vessels

Kidneys

Heart

CNS

↑ Vasoconstriction

↑ Inflammation

↑ Atherosclerosis

↑ Hypertrophy

↑ Fibrosis

↑ Na⁺ reabsorption

↑ Aldosterone effects

↑ Vasoconstriction

↑ Sympathetic activity
Angiotensin II type 1 receptor antagonists: an overview

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Possible Side effects</th>
<th>Some Potential interactions</th>
<th>Precautions and Contraindications</th>
</tr>
</thead>
</table>
| Candesartan       | • Hypertension • Intolerance to ACE inhibitor • Post-MI patients (secondary prevention of MI in patients with HF) | • Hypotension • Headache • Dizziness • Lightheadedness • Anemia • Fatigue • Hypoglycemia • Hyperkalemia • Angioedema • ↑ BUN • ↑ Serum creatinine | • Digoxin • Lithium • MAO inhibitors • NSAIDs • Potassium-sparing diuretics | Precautions: • Impaired renal/ hepatic function • Unilateral renal artery stenosis • Aortic/ mitral valve stenosis • Should not be used in combination with ACEI unless heart failure with recent hospitalization  
Contraindications: • Hypersensitivity • Pregnancy/ lactation • Bilateral renal artery stenosis |
| Eprosartan        | Additional Irbesartan / Losartan • HTN plus diabetic nephropathy              |                        |                             |                                   |
| Telmisartan       |                                                                              |                        |                             |                                   |
| Irbesartan        |                                                                              |                        |                             |                                   |
| Losartan          |                                                                              |                        |                             |                                   |
| Valsartan         |                                                                              |                        |                             |                                   |

ACEI: Angiotensin-converting enzyme inhibitor; ARBs: Angiotensin II receptor blockers; BUN: Blood urea nitrogen; HF: Heart failure; HTN: Hypertension; MAO: Monoamine oxidase; MI: Myocardial infarction; NSAIDs: Nonsteroidal anti-inflammatory drugs
Candesartan cilexetil

- Candesartan is poorly absorbed after oral administration, therefore the ester prodrug candesartan cilexetil was prepared. Candesartan cilexetil is an ester carbonate benzimidazole prodrug that has been designed by Takeda Ltd. and jointly developed with Astra-Zeneca.

- Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis and absorbed from the gastrointestinal tract to candesartan, a selective angiotensin II type 1 receptor antagonist. Candesartan is mainly excreted unchanged in urine and feces (via bile). It undergoes minor hepatic metabolism by o-de-ethylation to an inactive metabolite. The elimination half-life of candesartan is approximately 9 hours.

- Candesartan cilexetil finds most significant clinical use in the treatment of **hypertension of all grades**. It is also used in the treatment of **congestive heart failure** and experimentally in preventive treatment of migraine.

Valsartan

- Investigators at Ciba (Novartis) in Switzerland employed a strategy to open up the imidazole ring and replace it with the acylated amino acid valine. The carboxyl moiety of the valine serves to preserve oral bioavailability with high affinity receptor binding. Thus, valsartan is a diacid. Valsartan does not require metabolic oxidation to achieve the maximum pharmacologic effect.

- Plasma levels peaked 2 hours after oral administration. Thereafter, plasma levels declined biexponentially with a terminal half-life of 7 hours. On average of 7.3% (capsule) and of 12.6% (solution) of the dose was excreted in the urine as the unchanged drug.

- Valsartan is used to treat hypertension, heart failure, and to reduce death for people with left ventricular dysfunction after having had a heart attack.

- Common side effects include feeling tired, dizziness, high blood potassium, diarrhea, and joint pain. Other serious side effects may include kidney problems, low blood pressure, and angioedema. Use in pregnancy may harm the baby and use when breastfeeding is not recommended.
Ca\textsuperscript{++} channel antagonists

- According to recommendations from the JNC8 members, Ca\textsuperscript{++} channel antagonists are a recommended choice for initial management of hypertension, either as monotherapy or as part of anti-hypertensive combination therapy.

- Ca\textsuperscript{++} channel antagonists are a heterogeneous substance group which inhibit L-type voltage-gated Ca\textsuperscript{++} channels, which are found in the cardiac muscle and in smooth muscles of arteries and veins, as well as in nonvascular smooth muscles cells and nonmuscle tissue. Blockade of these Ca\textsuperscript{++} channels results in vasodilatation with lowering of blood pressure. Additionally, a negative inotropic effect is exerted on cardiac muscle. Some Ca\textsuperscript{++} antagonists bind more selectively to receptors in blood vessels (nifedipine, nisoldipine, and isradipine), whereas verapamil binds equally well to cardiac and vascular L-type Ca\textsuperscript{++} channels.
Ca\(^{++}\) channel blockers: an overview

- Calcium channel blockers are generally classified into three groups:

  1) dihydropyridines (amlodipine, eledipine, nicardipine, nifedipine, bepridil, felodipine, isradipine, and nisoldipine);

  2) phenylalkylamines (verapamil);

  3) benzothiazepines (diltiazem).

<table>
<thead>
<tr>
<th>Calcium channel blockers</th>
<th>Amlodipine, clevidine, nicardipine, nifedipine, nimodipine (dihydropyridines, act on vascular smooth muscle); diltiazem, verapamil (non-dihydropyridines, act on heart).</th>
</tr>
</thead>
<tbody>
<tr>
<td>MECHANISM</td>
<td>Block voltage-dependent L-type calcium channels of cardiac and smooth muscle → ↓ muscle contractility.</td>
</tr>
<tr>
<td></td>
<td>Vascular smooth muscle—amlodipine = nifedipine &gt; diltiazem &gt; verapamil.</td>
</tr>
<tr>
<td></td>
<td>Heart—verapamil &gt; diltiazem &gt; amlodipine = nifedipine (verapamil = ventricle).</td>
</tr>
<tr>
<td>CLINICAL USE</td>
<td>Dihydropyridines (except nimodipine): hypertension, angina (including Prinzmetal), Raynaud phenomenon.</td>
</tr>
<tr>
<td></td>
<td>Nimodipine: subarachnoid hemorrhage (prevents cerebral vasospasm).</td>
</tr>
<tr>
<td></td>
<td>Nicardipine, clevidine: hypertensive urgency or emergency.</td>
</tr>
<tr>
<td></td>
<td>Non-dihydropyridines: hypertension, angina, atrial fibrillation/flutter.</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>Non-dihydropyridine: cardiac depression, AV block, hyperprolactinemia, constipation.</td>
</tr>
<tr>
<td></td>
<td>Dihydropyridine: peripheral edema, flushing, dizziness, gingival hyperplasia.</td>
</tr>
</tbody>
</table>
Therapeutical uses of Ca^{++} channel blockers

- **angina pectoris**
  (verapamil, diltiazem),
- **cardiac failure**
  (verapamil, diltiazem,
  amlodipine, nisoldipine),
- **dysrhythmias** (verapamil,
  diltiazem),
- **hypertensions**
  (dihydropyridines),
- **migraine** (verapamil),
- **stroke** (nimodipine).
Side effects of $\text{Ca}^{++}$ channel blockers

<table>
<thead>
<tr>
<th><strong>Adverse Events</strong></th>
<th><strong>Calcium Channel Blockers</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common</td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
</tr>
<tr>
<td></td>
<td>Leg edema</td>
</tr>
<tr>
<td></td>
<td>Flushing</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Palpitation</td>
</tr>
<tr>
<td></td>
<td>Weakness</td>
</tr>
<tr>
<td>Other significant effects</td>
<td>Myocardial ischemia or infarction due to “coronary steal” hypotension</td>
</tr>
</tbody>
</table>
Nifedipine

- Nifedipine, prototype of the dihydropyridines, blocks selectively the Ca$^{++}$ channels in blood vessels. By inhibiting the influx of Ca$^{++}$ in smooth muscle cells, nifedipine prevents Ca$^{++}$-dependent myocyte contraction and vasoconstriction.

- The elimination half-life of nifedipine is approximately 2 hours. Nifedipine is almost completely absorbed from the gastrointestinal tract as shown by plasma levels after sublingual, oral, and rectal administration. Because of presystemic metabolism, the bioavailability is about 56% to 77%.

- Nifedipine is approved for the long-term treatment of hypertension and angina pectoris. Nifedipine has been used frequently as a tocolytic (agent that delays premature labor). Raynaud's phenomenon, in which spasm of arteries cause episodes of reduced blood flow, is often treated with nifedipine.

- Nifedipine rapidly lowers blood pressure, and patients are commonly warned they may feel dizzy or weak after taking the first few doses. Tachycardia may occur as a reaction. These problems are much less frequent in the sustained-release preparations of nifedipine. Extended release formulations of nifedipine should be taken on an empty stomach, and patients are warned not to consume anything containing grapefruit or grapefruit juice, as they raise blood nifedipine levels.
α1-antagonists

- α1-antagonists are used as a second choice drugs in the therapy of hypertension. They are able to occupy the binding site for the noradrenaline released by sympathetic nerves synapsing on smooth muscle.

- This blockade inhibits the smooth muscle contraction and lowers the blood pressure.

- Newer α-antagonists used in treating hypertension are relatively selective α1-adrenoceptor antagonists (e.g., prazosin, terazosin, doxazosin, trimazosin), whereas some older drugs are non-selective antagonists (e.g., phentolamine, phenoxybenzamine).
**α1-antagonists: an overview**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Possible Side effects</th>
<th>Some Potential Interactions</th>
<th>Precautions and Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective Alpha-adrenoceptor antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prazosin</td>
<td>Resistant hypertension</td>
<td>Hypotension</td>
<td>Amphetamines</td>
<td><strong>Precautions:</strong> Angina, Cataract surgery, Pregnancy/lactation</td>
</tr>
<tr>
<td>Terazosin</td>
<td>Pheochromocytoma</td>
<td>Palpitation</td>
<td>PDE-5 inhibitors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Benign prostatic hyperplasia</td>
<td>Headache</td>
<td>Prostacyclin analogues</td>
<td></td>
</tr>
<tr>
<td>Doxazosin</td>
<td>Additional Prazosin</td>
<td>Dizziness</td>
<td></td>
<td><strong>Contraindications:</strong> Hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>PTSD</td>
<td>Drowsiness</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Raynaud’s syndrome</td>
<td>Weakness</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-selective Alpha-adrenoceptor antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phentolamine</td>
<td>Hypertensive crises due to catecholamine</td>
<td>As Above</td>
<td></td>
<td><strong>Precautions:</strong> Cardiac arrhythmias, Peptic ulcer disease, Gastritis, Pregnancy/lactation</td>
</tr>
<tr>
<td></td>
<td>Diagnosis of pheochromocytoma</td>
<td></td>
<td></td>
<td><strong>Contraindications:</strong> Hypersensitivity, Renal impairment, Coronary or cerebral arteriosclerosis, MI (active or history), Concurrent use with PDE-5 inhibitors</td>
</tr>
<tr>
<td></td>
<td>Hypertension due to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pheochromocytoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pralidoxime</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MI:** Myocardial infarction; **PDE-5 inhibitors:** Phosphodiesterase 5 inhibitors; **PTSD:** Posttraumatic stress disorder
Doxazosin

- Doxazosin is a long-acting α1-antagonist structurally related to prazosin and terazosin.
- After both oral and intravenous administration, doxazosin is extensively metabolized, with only about 5% of the administered dose excreted unchanged in urine. Plasma elimination of doxazosin is biphasic, with a terminal elimination half-life of about 22 hours. Clearance of doxazosin is operated in the liver.
- Doxazosin finds most significant clinical use in the treatment of mild to moderate hypertension. In benign prostatic hyperplasia, doxazosin's effect of relieving bladder outflow obstruction is produced through a reduction in prostatic tone mediated via α1 antagonism. Doxazosin has also been used successfully in combination with β-blockers, diuretics, Ca++ channel antagonists, and ACE inhibitors in patients with hypertension that is uncontrolled with monotherapy. Doxazosin has a beneficial effect on some of the risk factors associated with coronary heart disease including elevated serum lipid levels, impaired glucose metabolism, insulin resistance and left ventricular hypertrophy.
- In acute and long term studies, doxazosin has an incidence of adverse effects and withdrawal rates similar to other α1-antagonists and other classes of antihypertensive agents. The most commonly reported adverse effects are dizziness, headache, fatigue/malaise and somnolence. Of most concern is the possibility of first-dose postural effects such as syncope.
Other anti-hypertensive drugs: vasodilators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Site of action</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium nitroprusside</td>
<td>Arterioles and veins</td>
<td>Production of nitric oxide</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Arterioles</td>
<td>Stimulation of NO release, Inhibition of Ca++ release from SR</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>Arterioles</td>
<td>K+ channel opening</td>
</tr>
<tr>
<td>Diazoxide</td>
<td>Arterioles</td>
<td>K+ channel opening</td>
</tr>
</tbody>
</table>
Other anti-hypertensive drugs: adrenergic drugs

Drugs

- Alpha-2 receptor agonists: clonidine
- Indirect acting adrenergic drugs: methyldopa

Mechanisms of antihypertensive action

a) Alpha-2 receptor agonists:
   - Activation of alpha-2 receptors in Nucleus Tractus Solitarius and in rostral ventrolateral medulla (the main mechanism).
   - Activation of peripheral alpha-2 receptors (after high doses).

b) Indirect acting adrenergic drugs:
   *Methyldopa* acts as a false neurotransmitter. It is taken up by the adrenergic neurons where it is transformed into methylnorepinephrine, the alpha-2 receptor agonist, which acts as described above.

The final effect common to all these drugs is a decreased firing of the reticulospinal tract, that is a decrease of central adrenergic tone.
Hypertensive emergencies

- Hypertensive emergencies are diagnosed when there is a systolic blood pressure higher than 180 mmHg or a diastolic blood pressure higher than 120 mmHg
  1) with the presence of acute target organ damage;
  2) in an otherwise stable person without clinical or laboratory evidence of acute target organ damage.

- Patients with hypertensive emergencies include:
  - dissecting aortic aneurysm,
  - acute pulmonary edema,
  - acute myocardial infarction,
  - unstable angina pectoris,
  - acute renal failure,
  - acute intracranial hemorrhage,
  - acute ischemic stroke,
  - hypertensive encephalopathy,
  - peri-operative hypertension,
  - sympathomimetic hypertensive crisis caused by use of cocaine, amphetamines, phencyclidine, or monoamine oxidase inhibitors or by abrupt cessation of clonidine or other sympatholytic drugs.

- These patients need effective and rapid acting medications administered intravenously to lower the elevated blood pressure safely, protect target organ function, ameliorate symptoms, reduce complications, and improve clinical outcomes.
# Management of hypertensive emergencies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Onset of action</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>20–40 mg i.v. injection in 1–2 min, repeated and higher doses with renal insufficiency</td>
<td>5–15 min</td>
<td>Volume depletion, hypokalemia</td>
</tr>
<tr>
<td><strong>Vasodilators</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>0.25–10 μg/kg/min as i.v. infusion</td>
<td>Within 30 sec</td>
<td>Nausea, vomiting, tachycardia, thiocyanate and cyanide intoxication</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>5–100 μg/min as i.v. infusion</td>
<td>2–5 min</td>
<td>Headache, vomiting, methemoglobinemia, tolerance with prolonged use</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>0.5–6 μg/kg/min as i.v. infusion</td>
<td>5–10 min</td>
<td>Headache, flushing, tachycardia, local phlebitis</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>10–20 mg i.v. injection</td>
<td>10–20 min</td>
<td>Headache, flushing, tachycardia, worsening of angina</td>
</tr>
<tr>
<td><strong>Sympathomlytics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labetalol</td>
<td>20–80 mg i.v. injection every 10 min; 2 mg/min as i.v. infusion</td>
<td>5–10 min</td>
<td>Nausea, vomiting, bronchospasm, heart block, orthostatic hypotension</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>1–10 mg i.v. injection, then 0.5–2 mg/min as i.v. infusion</td>
<td>1–2 min</td>
<td>Headache, flushing, tachycardia</td>
</tr>
</tbody>
</table>
Hypertension and comorbidities

<table>
<thead>
<tr>
<th>Characteristic (Number and %)</th>
<th>Hypertension</th>
<th>Hypertension and Diabetes mellitus</th>
<th>Hypertension and Hyperlipidemia</th>
<th>Hypertension and Coronary heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1146218 (54.00)</td>
<td>209121 (54.44)</td>
<td>108929 (55.63)</td>
<td>163156 (54.44)</td>
</tr>
<tr>
<td>Female</td>
<td>976485 (46.00)</td>
<td>174984 (45.56)</td>
<td>86876 (44.37)</td>
<td>136538 (45.56)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-44</td>
<td>265554 (12.51)</td>
<td>15222 (3.96)</td>
<td>20557 (10.50)</td>
<td>7444 (2.48)</td>
</tr>
<tr>
<td>45-59</td>
<td>653872 (30.80)</td>
<td>100263 (26.10)</td>
<td>62154 (31.74)</td>
<td>56712 (18.92)</td>
</tr>
<tr>
<td>60+</td>
<td>1203277 (56.69)</td>
<td>268620 (69.93)</td>
<td>113094 (57.76)</td>
<td>235538 (78.59)</td>
</tr>
</tbody>
</table>

Values in parentheses referred to the percentage of patients in the corresponding group.
Drugs used in hypertension with comorbidities

<table>
<thead>
<tr>
<th>HTN with:</th>
<th>Suitable Drug(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>Beta blockers, CCBs</td>
</tr>
<tr>
<td>Diabetes</td>
<td>ACE inhibitors, ARBs</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>ACE inhibitors, ARBs, Beta blockers</td>
</tr>
<tr>
<td>Post-MI</td>
<td>Beta blockers</td>
</tr>
<tr>
<td>BPH</td>
<td>Alpha blockers</td>
</tr>
<tr>
<td>Dyslipidemias</td>
<td>Alpha blockers, CCBs, ACE inhibitors/ARBs</td>
</tr>
</tbody>
</table>

Abbreviations: HTN: hypertension; CCBs: Calcium channel blockers; BPH: Benign prostatic hyperplasia; ARBs: Angiotensin receptor blockers; MI: Myocardial infarction.
Moving from a less intensive to a more intensive therapeutic strategy should be done whenever BP target is not achieved.
Possible combinations of classes of anti-hypertensive drugs.

Green continuous lines: preferred combinations; green dashed line: useful combination (with some limitations); black dashed lines: possible but less well-tested combinations; red continuous line: not recommended combination.

ACE = angiotensin-converting enzyme.