Clinical pharmacy in cardiology

Essential hypertension
Symptomatic hypertension
Clinical pharmacology of antihypertensive drugs

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Statistic of heart diseases (WHO 2009)

- Hypertensive Heart Disease: 21%
- Valvular Heart Disease: 17%
- Coronary Artery Disease: 19%
- Dilated Cardiomyopathy: 9%
- Other: 5%
Arterial Hypertension

- Arterial hypertension (AH) is a persistent increase of systolic and/or diastolic blood pressure above 140/90 mm Hg.

- It is well known that the main cause of many CVD is Hypertension.
- Complication of AH include stroke, myocardial infarction, heart failure, renal failure and others.
### Classification of European Society of Hypertension (ESH)

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>optimal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>normal</td>
<td>120–129</td>
<td>80–84</td>
</tr>
<tr>
<td>High normal</td>
<td>130–139</td>
<td>85–89</td>
</tr>
<tr>
<td>Grade 1 hypertension (mild)</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Grade 2 hypertension (moderate)</td>
<td>160–179</td>
<td>100–109</td>
</tr>
<tr>
<td>Grade 3 hypertension (severe)</td>
<td>≥180</td>
<td>≥110</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>≥160</td>
<td>&lt;90</td>
</tr>
</tbody>
</table>
• WHO identified hypertension as one of the most important preventable causes of premature morbidity and mortality in developed and developing countries
• It is the most prevalent cardiovascular disorder, affecting 20–30% of the adult population in developed countries
• The prevalence of hypertension increases with age, rising steeply after the age of 50, and affecting more than 50% of this population
Arterial Hypertension

- 90-95% of AH is **essential hypertension**
- There is no underlying medical illness to cause hypertension (“without cause”)
- In essential hypertension impairment pressor and depressor mechanism, it is accompanied by the injury of target organs

- 5-10% of AH is **secondary (symptomatic) hypertension**
- It is a hypertension caused by diseases of the organs involved in the blood pressure regulation
Symptomatic hypertension

- **Kidney diseases** (glomerulonephritis, pyelonephritis, congenital anomalies of the kidney, others)
- **Endocrine diseases** (pheochromocytoma, Conn’s disease, Cushing’s disease, Graves’ disease, climacteric, others)
- **Vascular diseases** (coarctation of the aorta)
- **Central origin** (meningitis, encephalitis, others)
- **Drug-induced hypertension** (corticosteroids, contraceptives, sympathomimetics, NSAIDs, etc.)
Hypertension is termed the “silent killer” because the most patients at the beginning do not have any symptoms. The primary physical finding is elevated BP.

The diagnosis of hypertension cannot be based on one elevated BP measurement. The average of two or more measurements taken during two or more clinical encounters should be used to diagnose hypertension.
• Headache, dizziness, nausea, vomiting, weakness

• Symptoms of stroke (paresis, plegia, loss of consciousness)

• Symptoms of hypertensive association diseases (obesity, diabetes mellitus, ischemic heart disease)

• Nasal bleeding
Diagnosis:

The British hypertension society in (2011 August) change the diagnosis for hypertension, the new 2011 guideline recommends that a diagnosis of primary hypertension should be confirmed using 24-hour ambulatory blood pressure monitoring (ABPM) as gold standard (published in the Lancet 24/08/11)
Hypertension is treated with:

A) Life style modifications
• Weight loss
• Physical activity
• Moderate alcohol consumption
• Diet rich with fruit, vegetable
• Reduction of dietary salt saturated fat content
• Increase dietary potassium intake
  • Cessation of smoking also useful (from observational studies)

B) Pharmacotherapy
Pharmacotherapy

Recommendation of WHO 2003 for the first line therapy of essential hypertension treatment:

- ACE inhibitors
- Angiotensin II receptors antagonists (Sartans)
- Beta-blockers
- Ca antagonists
- Diuretics
Angiotensinogen 

Angiotensin I 

Angiotensin II 

Renin 

DRI 

Non ACE enzymase (Chymase) 

ACE 

ACE Inh 

Bradykinin 

Inactivate metabolites 

AT₁ receptors 

AT₂ receptors 

ARBs 

Aldosterone release 

Myocardial and vascular fibrosis 

Sodium and water retention, potassium loss 

Vasoconstriction, increased preload and afterload 

PCs 

NO 

O₂ 

PAI-1 tPA 

LOX-1 expression 

cough
Angiotensin converting enzyme inhibitors

• In 1954, Skeggs and coworkers started to recognize substrates participating in the renin–angiotensin system.

• In 1956, they purified the enzyme responsible for the conversion of inactive angiotensin I to the active vasoconstrictor angiotensin II from horse plasma.

• By early 1974, the efficacy of ACE inhibitors as antihypertensive drugs had been demonstrated, but they were not yet available in an oral form.

• In the early 1980s, Squibb succeeded in developing an oral form known as Captopril (Capoten) and received approval from the USA Food and Drug Administration for this drug.

• In the early 1970s Nobel laureate John Vane also played a key role in research that led to the discovery of Captopril – the first member of the ACE inhibitor
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**
## Representatives of ACE inhibitors in the pharmaceutical market

<table>
<thead>
<tr>
<th>International name</th>
<th>Trade name</th>
<th>Manufactured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>Capoten®</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Vasotec®, Renitec®, Enalapril Maleate Enalapril Enap</td>
<td>Merck Sharp Dhome Teva Pharmaceuticals, Ranbaxy Pharmaceuticals Actavis KRKA</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>Monopril®, Fosinopril sodium</td>
<td>Bristol-Myers Squibb Company Sandoz</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Prinivil®, Zestril Lisinopril Diroton</td>
<td>Merck AstraZeneca Teva Pharmaceuticals Gedeon Richter</td>
</tr>
<tr>
<td>Moexipril</td>
<td>Univasc®</td>
<td>UCB Pharmafor Schwarz Pharma</td>
</tr>
<tr>
<td>Perindopril</td>
<td>Aceon®</td>
<td>Solvay Pharmaceuticals</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Accupril®</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Benazepril</td>
<td>Lotrel®, Lotensin®, Fortekor®</td>
<td>Novartis Pharmaceuticals</td>
</tr>
<tr>
<td>Ramipril</td>
<td>Altace®</td>
<td>Sanofi Aventis</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>Mavik®</td>
<td>Abbott Laboratories</td>
</tr>
</tbody>
</table>
Side effects of ACE inhibitors

- Cough (5% of patients),
- Elevated blood potassium levels,
- Low blood pressure, dizziness, headache,
- Drowsiness, weakness,
- Abnormal taste (metallic or salty taste),
- Rash, angioneurotic edema (sporadic)
- Syndrome of the first dose
Angiotensin II antagonists or angiotensin II receptor blockers (ARBs) inhibit the action of AT$_1$ receptors and they suppress the effects of angiotensin II: vasoconstriction, vascular and cardiac hypertrophy and stimulation of aldosterone secretion.

The first inhibitors of AT$_1$ receptors, like Saralasin, were not adapted to therapeutic use because they were not active by oral route.

Losartan was the first AT$_1$ antagonist active by oral route. Losartan is an active molecule but one of its metabolites is more active.
Representatives of ARBs in the pharmaceutical market

<table>
<thead>
<tr>
<th>International name</th>
<th>Trade name</th>
<th>Manufactured</th>
</tr>
</thead>
<tbody>
<tr>
<td>losartan</td>
<td>Cozaar®</td>
<td>Merck &amp; Co. Pharm.</td>
</tr>
<tr>
<td>Candesartan</td>
<td>Atacand®</td>
<td>AstraZeneca LP.</td>
</tr>
<tr>
<td>Valsartan</td>
<td>Diovan®</td>
<td>Novartis Pharmaceuticals Inc.</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>Avapro®</td>
<td>Bristol-Myers Squibb.</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>Micardis®</td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>Teveten®</td>
<td>Solvay Healthcare Limited</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>Benicar®</td>
<td>Daiichi Sankyo</td>
</tr>
<tr>
<td>Azilsartan</td>
<td>Edarbi®</td>
<td>Takeda Pharmaceuticals America</td>
</tr>
</tbody>
</table>

**FIGURE 2 SHARE OF TOTAL ARB PRESCRIPTIONS**
November 2011

- losartan/HCT: 38%
- Diovan/HCT: 31%
- Avapro/Avalide: 5%
- Benicar/HCT: 12%
- Micardis/HCT: 4%
- Exforge/HCT: 4%
- All others: 6%

Source: IMS Health, IMS National Prescription Audit™, 11/2011
Side effects of sartans

Adverse effects of ARBs are mild and not frequent

- Hypotension and hyperkalemia rarely
- They do not cause cough and angioedema
- Their use during pregnancy is contraindicated: the first trimester for a possible teratogenic risk and during second and third trimesters because of the risk of oligoamnios, fetal renal impairment, fetal death
- Do not decrease mortality due heart failure such as ACE inhibitors (so not included in every guideline of treatment of heart failure)
• NEW class of antihypertensive drug: Aliskiren in dose 150-300 mg/daily
• Contraindicated in bilateral renal artery stenosis
• Aliskiren is metabolized by the cytochrome P450-3A4 enzyme, so serum concentrations of furosemide are significantly reduced
• Could lead to allergic reaction such as angioedema
• Contraindicated in first trimester of pregnancy
Beta blockers

- Sir James Black developed the first beta blocker in 1962.
- This drug was approved by the FDA in 1968.
- The Nobel Prize in Medicine was awarded to Sir Black in 1988 for this discovery.
Mechanism of action

- block the action of endogenous catecholamines (adrenaline and noradrenaline) on β-adrenergic receptors, part of the sympathetic nervous system.

Beta receptors

β1-
- heart
- kidneys

β2-
- lungs
- gastrointestinal tract
- liver
- uterus
- vascular smooth muscle
- skeletal muscle

β3-
- fat cells
Beta-blockers

- **Cardiac effects**
  - Decrease contractility (negative inotropy)
  - Decrease relaxation rate (negative lusitropy)
  - Decrease heart rate (negative chronotropy)
  - Decrease conduction velocity (negative dromotropy)

- **Vascular effects**
  - Smooth muscle contraction (mild vasoconstriction)
Indication for beta-blockers

- Arterial hypertension (essential, secondary in thyrotoxicosis, pheochromocytoma)
- Arrhythmias (tachycardia, extrasystolia)
- Ischemic heart disease (CAD)
- Chronic heart failure (beta-blockers in small dose)
- Glaucoma
- Migraine
- Panic attack
Selectivity of different beta-blockers
Side effects of beta-blockers

- Bradycardia
- Withdraw syndrome
- Prolong atrioventricular conduction (A/V block)
- Peripheral vasoconstriction
- Mask hypoglycemia (increase of plasma glucose)
- Increase of plasma lipids
- Bronchospasm
- Contract of uterus
- Erectile dysfunction (impotence)
- Sleep disturbances (decrease melatonin)
Antagonists of calcium

- **derivatives fenilalkilamina** - verapamil
  (finoptin, Isoptin, lekoptin)

- **benzothiazepine derivatives** - diltiazem
  (cardio, dilzem)

- **dihydropyridine derivatives** - Nifedipine
  (korinfar, fenigidin, kordafen,)
  amlodipine (Norvasc), Lacidipin (latsipil),
  lercanidipine (lerkamen), nimodipine (Nimotop),
  felodipine (felogeksal).
Special condition of dihydropyridine derivatives

• one antihypertensive drug that is recommended for pregnant women
• Advisable in patients with diabetes mellitus
• preferably prescribe elderly patients, especially in isolated systolic hypertension
• contraindicated in extrasystolic arrhythmia and tachycardia
Side effects of dihydropyridine derivatives

- hypotension;
- redness of the face and neck (flushing);
- headache;
- tachycardia (nifedipine);
- constipation;
- swelling of the legs
Diuretics

- **Thiazide** (hypotiazide, indapamide)
- Potassium-sparing (spironolactone)
- Loop (furosemide)
## Figure 1: Hypertension Market Performance

<table>
<thead>
<tr>
<th>Class of Drugs</th>
<th>Total Rx’s</th>
<th>Share of HTN Market</th>
<th>Sales</th>
<th>Share of HTN Market</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>164.8 million</td>
<td>30%</td>
<td>$1.2 billion</td>
<td>9%</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>127.5 million</td>
<td>24%</td>
<td>$1.9 billion</td>
<td>14%</td>
</tr>
<tr>
<td>Calcium channel blockers (CCBs)</td>
<td>98.1 million</td>
<td>18%</td>
<td>$1.4 billion</td>
<td>10%</td>
</tr>
<tr>
<td>ARBs (includes ARB/CCB and other ARB combination products)</td>
<td>83.4 million</td>
<td>15%</td>
<td>$7.4 billion</td>
<td>53%</td>
</tr>
<tr>
<td>Alpha/beta-blockers</td>
<td>25.2 million</td>
<td>5%</td>
<td>$418.1 million</td>
<td>3%</td>
</tr>
<tr>
<td>All others</td>
<td>42.5 million</td>
<td>8%</td>
<td>$1.6 billion</td>
<td>11%</td>
</tr>
</tbody>
</table>

Sources: IMS Health, IMS National Prescription Audit™, IMS National Sales Perspectives™, MAT 11/2011
The British hypertension society recommendation (2011 august)

- **Primary:**
  - diuretic (D) primarily a thiazide
  - ACE inhibit or, angiotensin II receptor blocker (ARB),
  - calcium channel blocker (CCB),
  - are considered primary antihypertensive agents that are acceptable first line options.

- **Secondary:**
  - \(\beta\)-blockers(B) preferred either to treat a specific compelling indication, or in combination with one of the aforementioned primary antihypertensive agents for patients without a compelling indication.
Hypertension treatment goals

- Patients with 10-year risk of CAD of <10%, based on Framingham scoring, have a goal BP of <140/90 mmHg
- For hypertension-associated complications, 130/85 mmHg and lowering BP to this level with diabetes or CRD
- If patients have a history of left ventricular dysfunction (LVD), a BP goal of <120/80 mmHg is recommended
Thank you for your attention!