Drugs in Hypertension

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Pharmacology Unit, FMS

Objectives

- Revision of physiological control of BP.
- What is hypertension? Associated risks of uncontrolled hypertension
- ANTIHYPERTENSIVE DRUGS:
  1. Sympathetic Nervous System inhibition
     - β-blockers, αi blockers, mixed α, β blockers, central α agonists, peripheral adrenergic blockers.
  2. Sodium/Renin Angiotensin Aldosterone System balance
     - Diuretics, ACE inhibitors, AT11 receptors blockers
  3. Vasodilators
     - Ca2+-channel blockers, oral and parenteral vasodilators

Mechanisms of action, other indications, contraindications and adverse effects
Hemodynamic factors affecting BP

Arterial Blood Pressure \( \approx \) Cardiac Output (CO) \( \times \) Total Peripheral Resistance (TPR)

- Heart rate
- Contractility
- Filling pressure
- Arteriolar volume
- Blood volume
- Venous tone

BP Regulation: SNS and RAAS

Baroreceptor reflex system mediated:
- \( \uparrow \beta_1 \) receptor cardiac activation
- \( \uparrow \alpha_1 \) receptor smooth muscle activation
- \( \downarrow \) sympathetic activity

Renal blood volume-pressure system:
- \( \downarrow \) Renal flow
- \( \uparrow \) renin
- \( \uparrow \) Angiotensin II
- \( \uparrow \) Aldosterone
- \( \downarrow \) GFR
- \( \uparrow \) Na\(^+\), H\(_2\)O retention
- \( \uparrow \) Blood volume

- \( \uparrow \) CO
- \( \uparrow \) TPR
- \( \uparrow \) BP
- \( \downarrow \) BP

Baroreceptor reflex system mediated:
- \( \uparrow \beta_1 \) receptor cardiac activation
- \( \uparrow \alpha_1 \) receptor smooth muscle activation
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- \( \uparrow \) Na\(^+\), H\(_2\)O retention
- \( \uparrow \) Blood volume

- \( \uparrow \) CO
- \( \uparrow \) TPR
- \( \uparrow \) BP
- \( \downarrow \) BP
What is hypertension?

<table>
<thead>
<tr>
<th>JNC 6 Category</th>
<th>JNC 7 Category (2004)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP/DBP (mmHg)</td>
</tr>
<tr>
<td>Optimal</td>
<td>&lt;120/80</td>
</tr>
<tr>
<td>Normal</td>
<td>120-129/80-84</td>
</tr>
<tr>
<td>Borderline</td>
<td>130-139/85-89</td>
</tr>
<tr>
<td>Hypertension</td>
<td>&gt;140/90</td>
</tr>
<tr>
<td>Stage 1</td>
<td>140-159/90-99</td>
</tr>
<tr>
<td>Stage 2 (moderate)</td>
<td>160-179/100-109</td>
</tr>
<tr>
<td>Stage 3 (severe)</td>
<td>≥180/110</td>
</tr>
</tbody>
</table>

A chronic disease of persistent elevated arterial blood pressure.

Classification

1º or essential hypertension (> 95%)
- Genetic
- Ethnic
- Lifestyle
- Gender and age

2º hypertension (~5%)
- Chronic renal disease
- Pheochromocytoma
- Cushing’s syndrome and glucocorticoid excess states
- 1º aldosteronism and other mineralocorticoid excess states
- Coarctation of the aorta
- Drug-induced
**Associated risks**

Chronic \( \uparrow \) arterial BP \( \uparrow \) likelihood of morbidity and mortality.

1. CAD
2. LVH
3. CHF
4. MI
5. Arrhythmias
6. Angina
7. Stroke
8. Dementia
9. Renal disease

*CVD risk doubles for each increment of 20/10 mmHg*

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**Why treat?**

- Treating hypertension:
  - ↓ stroke by 40% - 45%
  - ↓ CHF by 40% - 50%
  - ↓ CAD by 16% - 25%

- >30% unaware
- Educational intervention ↓ BP.
- In UK, only ~6% adequately treated.
Drug classification

**SNS inhibition**
- **β antagonists**
- **Mixed α,β antagonists**
- **Central α, agonists**
- **α1 antagonists**
- **Peripheral adrenergic antagonists**

**Sodium/RAAS balance**
- **Diuretics**
- **ACE Inhibitors**
- **ATII antagonists**

**Vasodilators**
- **Ca²⁺ channel blockers**
- **Others**

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**β antagonists**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name(s)</th>
<th>Doses available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>Inderal®</td>
<td>Oral: 10, 20, 40, 60, 80, 90mg; 4, 8mg/mL oral soln; Inderal LA: 80, 80, 120, 160mg Parenteral: 1mg/mL soln</td>
</tr>
<tr>
<td>Nadolol</td>
<td>Corgard®</td>
<td>Oral: 20, 40, 80, 120, 160mg</td>
</tr>
<tr>
<td>Pindolol</td>
<td>Visken®</td>
<td>Oral: 5, 10mg</td>
</tr>
<tr>
<td>Acebutolol (*)</td>
<td>Sectral®</td>
<td>Oral: 200, 400mg</td>
</tr>
<tr>
<td>Metoprolol (*)</td>
<td>Toprol®, Lopressor®</td>
<td>Oral: 50, 100mg; XL: 25, 50, 100, 200mg Parenteral: 1mg/mL soln</td>
</tr>
<tr>
<td>Atenolol (*)</td>
<td>Tenormin®</td>
<td>Oral: 25, 50, 100mg; Parenteral: 0.5mg/mL soln</td>
</tr>
<tr>
<td>Betaxolol (*)</td>
<td>Kerlone®</td>
<td>Oral: 10, 20mg</td>
</tr>
<tr>
<td>Bisoprolol (*)</td>
<td>Zebeta®</td>
<td>Oral: 5, 10mg</td>
</tr>
</tbody>
</table>

(*) cardioselective
**Mechanism of Action**

**Acute effect**
- $\beta_1$ blockade in myocardial cells
  - $\downarrow$ CO
  - Shift in whole body autoregulation

**Long term effect**
- $\beta_1$ blockade in juxtaglomerular cells
  - $\downarrow$ aldosterone
  - $\downarrow$ Na$^+$ retention
  - $\downarrow$ Blood volume
  - $\downarrow$ Renin release
  - $\downarrow$ [Angiotensin II]$_{\text{plasma}}$
  - $\downarrow$ arterial vasoconstriction
  - Change in arterial remodelling

$\downarrow$ TPR

$\downarrow$ BP

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**Other Indications**

- Angina pectoris
- Arrhythmias
- Glaucoma (applied topically)
- Migraine
- IHD and prevention of 2nd MI.

Useful as monotherapy in Stage 1 HTN or with vasodilators (and diuretics) in stage 2.
**Contraindications**

- CHF and nodal conduction diseases.
  - But, carvedilol (Coreg®), misoprolol and metoprolol ↓ mortality in CHF

- Non-selective β blockers in asthma. Cardio-selective drugs lose selectivity at higher doses.

- Use with caution in insulin-dependent diabetic patients.
  - Glycogenolysis is adrenergically mediated. β blockers antagonize sympathetic response to hypoglycemia and blunt recovery.

**Adverse Effects**

- CNS: Sedation, depression, lethargy, sleep disturbances

- CV: CHF in LV dysfunction, heart block, bradyarrhythmias

- Bronchospasms (non-selective blockers) in asthma and COPD.

- ↓HDL and ↑plasma triacylglycerol

- Abrupt cessation may induce unstable angina, MI or death in patients predisposed to ischemic myocardial events. Taper over 14 days.
**α_1 antagonists**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name(s)</th>
<th>Doses available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prazosin</td>
<td>Minipress®</td>
<td>Oral: 1, 2, 5mg</td>
</tr>
<tr>
<td>Terazosin</td>
<td>Hytrin®</td>
<td>Oral: 1, 2, 5, 10mg</td>
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<tr>
<td>Doxazosin</td>
<td>Cardura®</td>
<td>Oral: 1, 2, 4, 8mg</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>Flomax®</td>
<td>Oral: 0.4mg</td>
</tr>
</tbody>
</table>

**Mechanism of Action:**
Arterial and venous relaxation - ↓ TPR; ↓ BP.
Minimal ↑ CO, renal blood flow or GFR. No long-term tachycardia and ↑ renin release.

**Indication:**
- Benign prostatic hypertrophy and hypertension (prostate capsule relaxation decreases resistance to urinary flow)

**Adverse Effects:**
1. 1st dose dizziness or syncope – give at bedtime (caution in elderly).
2. Initial reflex tachycardia (propranolol to counteract)
3. Postural hypotension
4. Infrequent and mild CNS: vivid dreams, lassitude and depression.
Mixed $\alpha$, $\beta$ antagonists

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name(s)</th>
<th>Doses available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td>Normodyne®</td>
<td>Oral: 100, 200, 300mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parenteral: 5mg/mL soln</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Coreg®</td>
<td>Oral: 3.125, 6.25, 12.5, 25mg</td>
</tr>
</tbody>
</table>

Labetalol

- Equimolar mixture of 4 stereoisomers:
  2 inactive, 1 $\alpha_1$-blocker, other non-selective $\beta$-blocker and $\beta_2$-partial agonist.
- Useful in hypertensive emergencies (as iv)
- Similar efficacy and side-effects as $\beta$- and $\alpha_1$-antagonists when given orally.

**Mechanism of action:**
1. $\alpha_1$ blockade and $\beta_2$ stimulation cause rapid vasodilatation, ↓ TPR leading to ↓BP

Contraindications same as non-selective $\beta$ blockers
Peripheral adrenergic antagonists

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name(s)</th>
<th>Doses available</th>
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<tbody>
<tr>
<td>Reserpine</td>
<td>-</td>
<td>Oral: 0.1, 0.25mg</td>
</tr>
<tr>
<td>Guanethidine</td>
<td>Ismelin®</td>
<td>Oral: 10, 25mg</td>
</tr>
<tr>
<td>Guanadrel</td>
<td>Hylorel®</td>
<td>Oral: 10, 25mg</td>
</tr>
</tbody>
</table>

**Reserpine: Mechanism of action**

1. Binds avidly to NE and 5-HT storage vesicles in central and peripheral adrenergic neurons inducing catecholamine leakage.

2. Overall Effect: Minimal active transmitter discharged from depolarized nerve endings.

3. Neurotransmitter depletion in brain and myocardium leads to sedation, depression and ↓CO.

*Rauwolfia serpentina* root used in Ayurvedic medicine, isolated in 1950’s and used in Western medicine.
Reserpine

- ↓CO, ↓TPR
- ↓HR, (Na+ and H2O retention)
- Low doses + diuretic ≡ diuretic + propranolol or methyldopa

Adverse Effects
1. CNS: Sedation, inability to concentrate, nightmares, dose-related psychotic depression – contraindicated in pre-existing depression.
2. Unabated parasympathetic activity - nasal stuffiness, ↑gastric acid secretion (contraindicated in peptic ulcer), diarrhea and bradycardia

Central α2 agonists

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name(s)</th>
<th>Doses available</th>
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<tbody>
<tr>
<td>Clonidine</td>
<td>Catapress®</td>
<td>Oral: 0.1, 0.2, 0.3mg Transdermal patch: 0.1, 0.2, 0.3mg/24hrs</td>
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<tr>
<td>Methyldopa</td>
<td>-</td>
<td>Oral: 250, 500mg</td>
</tr>
<tr>
<td>Guanabenz</td>
<td>Wytensin®</td>
<td>Oral: 4, 8mg</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>Tenex®</td>
<td>Oral: 1, 2mg</td>
</tr>
</tbody>
</table>
**Mechanism of action**

- Selective $\alpha_2$ agonists in the CNS:
  - $\downarrow$ CNS sympathetic outflow – enhanced parasympathetic activity - $\uparrow$ vagal tone - $\downarrow$ BP

- $\downarrow$HR, $\downarrow$CO, $\downarrow$ TPR, $\downarrow$ plasma renin, blunted baroreceptor reflexes.

- $\downarrow$ NE plasma levels directly $\downarrow$ TPR with $\downarrow$ BP.

Clonidine useful in pheochromocytoma diagnosis

**$\infty$-Methyldopa**

- Drug of choice in this class; usefulness limited by adverse effects.

- Chronic use results in $\text{Na}^+$ and fluid retention (diuretic).

- Metabolized to its active form ($\alpha$-methylnorepinephrine) in the brain
**∞- Methyldopa**

- $t_{1/2}$: 2hrs; peak effect: ~6-8hrs; Duration of action: ~24hr
- In elderly: ↓HR and ↓stroke volume resulting in ↓CO, in young uncomplicated patient no such effect.
- Adverse effects:
  - Sedation, lassitude, nightmares, depression, vertigo, galactorrhea (men & women).

**Clonidine**

- ↓CO and ↓TPR
- ↓cardiac sympathetic tone leads to ↓iontropy, ↓chronotropy

**Adverse Effects:**
1. CNS – Sedation; avoid in depression
2. Dry mouth

**Not 1st line therapy**
Clonidine

**Caution:**

Dose-related withdrawal syndrome within 18-36 hrs; sympathetic discharge leading to rebound hypertension or overshoot hypertension.

Symptoms: headache, apprehension, tremors, abdominal pain, sweating, and tachycardia.

ACE Inhibitors

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name(s)</th>
<th>Doses available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>Vasotec®</td>
<td>Oral: 2.5, 5, 10, 20mg</td>
</tr>
<tr>
<td>Captopil</td>
<td>Capoten®</td>
<td>Oral: 12.5, 25, 50, 100mg</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Zestril®, Prinivil®</td>
<td>Oral: 2.5, 5, 10, 20, 40mg</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>Monopril®</td>
<td>Oral: 10, 20, 40mg</td>
</tr>
<tr>
<td>Benazepril</td>
<td>Lotensin®</td>
<td>Oral: 5, 10, 20, 40mg</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Accupril®</td>
<td>Oral: 5, 10, 20, 40mg</td>
</tr>
</tbody>
</table>
### Renin-Angiotensin-Aldosterone System

![Diagram of the Renin-Angiotensin-Aldosterone System]

- **Angiotensinogen**
- **Renin**
- **Angiotensin I**
- **Angiotensin Converting Enzyme**
- **Angiotensin II**
- **Aldosterone**
- **Vasoconstriction**
- **↑ Na⁺, H₂O retention**
- **↑ Blood volume**
- **↑ CO**
- **x**
- **↑ TPR**
- **↑ BP**

**ACE inhibitors** block bradykinin degradation, stimulate PE₂ & prostacyclin.

### ACE Inhibitors

- **As effective as diuretics and β-blockers**
- **Supervise 1st dose**
- **↓ TPR without reflex ↑ CO, HR or inotrophy**
- **Fetotoxic** (absolutely contraindicated in pregnancy)

**Initiate with very low dose with slow titration.**
Other Indicators

- CHF (↓ nonfatal and fatal events).
- LVH (may prevent or partial regression).
- Type 1 diabetic nephropathy

Adverse Effects

- Acute hypotension (at onset, esp in severe Na⁺ & volume depletion)
- Skin rash (sometimes transient)
- Cough (10% - 20%)

To a lesser extent (<1%):
- Hematologic toxicity: neutropenia, agranulocytosis
- Angioedema – more in Africans
- Acute renal failure – esp. in unilateral/bilateral renal artery stenosis
- Glomerulonephritis
- Proteinuria (captopril)
- Hyperkalemia – esp. in renal disease, DM, on NSAIDs, K⁺ supp. or K⁺-sparing diuretics
- Fever
# Angiotensin II receptor antagonists

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name(s)</th>
<th>Doses available</th>
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<tbody>
<tr>
<td>Losartan</td>
<td>Cozaar®</td>
<td>Oral: 25, 50, 100mg</td>
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<tr>
<td>Valsartan</td>
<td>Diovan®</td>
<td>Oral: 40, 80, 160, 320mg</td>
</tr>
<tr>
<td>Candesartan</td>
<td>Atacand®</td>
<td>Oral: 4, 8, 16, 32mg</td>
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<tr>
<td>Olmesartan</td>
<td>Benicar®</td>
<td>Oral: 5, 10, 20, 40mg</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>Micardis®</td>
<td>Oral: 20, 40, 80mg</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>Avapro®</td>
<td>Oral: 75, 150, 300mg</td>
</tr>
</tbody>
</table>

## Mechanism of Action

**Blockade of AgII receptors**
- ↓ vasoconstriction
- ↓ Na⁺ retention
- ↓ TPR
- ↓ BP
- ↓ CO

### Acute effect
- Ag II
- Stimulation of arterial wall growth
- ↑ wall to lumen ratio (remodelling)
- ↑ vasoconstriction

### Long term effect
- No effect on bradykinin breakdown
Angiotensin II receptor subtypes

- AT$_1$ (site of action of ATII antagonists)
  - Vasoconstriction
  - Aldosterone release
  - Sympathetic activation
  - ADH release
  - Constriction of efferent glomerular arterioles

- AT$_2$ (beneficial effect not blocked)
  - Vasodilation

AgII also produced by enzymic reactions of chymases

Other Indications

- "ACE inhibitor without the cough"
- Heart failure
- Intolerance to other hypertensive drugs

All have similar antihypertensive efficacy with flat dose-response curve
Adverse Effects

- Renal insufficiency (↓glomerular perfusion pressure)
- Hyperkalemia

Caution: History of ACE inhibitor-induced angioedema

Diuretics

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name(s)</th>
<th>Available doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorothiazide</td>
<td>Diuril®</td>
<td>Oral: 250, 500; 250mg/mL oral suspension</td>
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<tr>
<td>Hydrochlorothiazide</td>
<td>Hydrodiuril®</td>
<td>Oral: 25, 50, 100mg tabs; 12.5mg capsules Parenteral: 10mg/mLsoln</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>Thalitone®</td>
<td>Oral: 250, 500 mg; 250 mg/5mL oral suspension</td>
</tr>
<tr>
<td>Indapamide</td>
<td>Lozol®, others</td>
<td>Oral: 1.25, 2.5mg</td>
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<tr>
<td>Metolazone</td>
<td>Zaroxolyn®</td>
<td>Oral: 0.5mg</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Lasix®</td>
<td>Oral: 20, 40, 80 mg; Parenteral: 10mg/mL</td>
</tr>
<tr>
<td>Bumetamide</td>
<td>Bumex®</td>
<td>Oral: 0.5, 1, 2 mg; Parenteral: 0.5mg/2mL</td>
</tr>
<tr>
<td>Torsemide</td>
<td>Demadex®</td>
<td>Oral: 5, 10, 15, 20mg; Parenteral: 10mg/mL</td>
</tr>
<tr>
<td>Ethacrynic Acid</td>
<td>Edecrin®</td>
<td>Oral: 25, 50mg; Parenteral: 50mg/mL</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Aldactone®</td>
<td>Oral: 25, 50, 100mg</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>Inspra®</td>
<td>Oral: 25, 50mg</td>
</tr>
<tr>
<td>Amiloride</td>
<td>Midamor ®</td>
<td>Oral: 5mg</td>
</tr>
<tr>
<td>Triamterene</td>
<td>Dyrenium®</td>
<td>Oral: 50, 100mg</td>
</tr>
</tbody>
</table>
**Diuretics – Thiazides (1st line)**

**Acute effect**
- Block renal tubule Na⁺-Cl⁻ reabsorption
- ↑ angiotensin II (↑ urinary loss of Na⁺ and H₂O)
- ↑ renin release
- ↓ extracellular volume

**Long term effect**
- • CO returns to normal
- • Slight ↓ in body Na⁺
- • Opening of K⁺ channels (hyperpolarization)
- ↓ [Ca²⁺] in vascular smooth muscle cells
- ↓ affinity of vascular smooth muscle cells for vasoconstrictor hormones
- ↓ Contractility of vascular smooth muscle cells

↓BP  ↓CO  ↓BP  ↓TPR  ↓CO  ↓BP

**Diuretics – Furosemide (not 1st line)**

**Acute effect**
- Binds to Cl⁻ binding site of Na⁺-K⁺-2Cl⁻ cotransporter in thick ascending loop of Henle
- ↑ Angiotensin II  ↑ loss of Na⁺ and H₂O
- ↑ Renin release
- ↓ Extracellular fluid volume

**Long term effect**
- • CO returns to normal
- • Slight ↓ in body Na⁺
- ↓ Contractility of VSMC

? ↓BP ?  ↓TPR
**Loop Diuretic – Furosemide**

**Indications:**
- Resistant hypertension (*not 1st line*)
- Edema (renal impairment or volume overload)
- Hypercalcemia
- Hyperkalemia

**Ca\(^{2+}\) channel blockers**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name(s)</th>
<th>Doses available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzothiazepine</td>
<td>Cardizem®</td>
<td>Oral: 30, 60, 90, 120mg; sustained release: 60, 90, 120, 180, 240, 300, 360, 420mg. Parenteral: 5mg/mL soln</td>
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<tr>
<td>Diltiazem</td>
<td></td>
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</tr>
<tr>
<td>Diphenylalkylamine</td>
<td>Calan®, Isoptin®</td>
<td>Oral: 40, 80, 120mg; sustained release: 120, 180, 240mg. Parenteral: 2.5mg/mL soln</td>
</tr>
<tr>
<td>Verapamil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydropyridine</td>
<td>Adalat® CC, Procardia® XL</td>
<td>Oral: 10, 20mg. Extended release: 30, 60, 90mg</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Norvasc®</td>
<td>Oral: 2.5, 5, 10mg</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Plendil®</td>
<td>Oral extended release: 2.5, 5, 10mg</td>
</tr>
<tr>
<td>Felodipine</td>
<td>DynaCirc®</td>
<td>Oral: 2.5, 5mg; controlled release: 5, 10mg</td>
</tr>
<tr>
<td>Isradipine</td>
<td>Cardene®</td>
<td>Oral: 20, 30mg; sustained release: 30, 45, 60mg. Parenteral: 2.5mg/mL soln</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Sular®</td>
<td>Oral extended release: 10, 20, 30, 40mg</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td></td>
<td></td>
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</tbody>
</table>
**Mechanism of Action**

**Dihydropyridines**
- Nifedipine, Amlodipine
  - Block L-type Ca\(^{2+}\) channels in arterial smooth muscle
  - \(\downarrow\) TPR
  - \(\downarrow\) BP
  - Baroreceptor-mediated reflex tachycardia

**Verapamil, Diltiazem**
- Block L-type Ca\(^{2+}\) channels in SA and AV node
  - \(\downarrow\) or abolishes reflex tachycardia

**Inhibit influx of Ca\(^{2+}\) ions thru’ voltage-gated channels**

**Relative efficacy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vasodilation (coronary flow)</th>
<th>-ve inotropy</th>
<th>Automaticity (SA node) suppression</th>
<th>AV conduction suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Verapamil</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

**Relative cardiovascular effect: 0=no effect, 5=maximum effect**
**Indications**

- Mild to moderate HTN associated with exercise-induced, variant and unstable angina.
- MI (ACE inhibitors>protective than dihydropyridines)
- Antiarrhythmic (diltiazem and verapamil for supraventricular tachycardia, atrial fibrillation and atrial flutter).

**Adverse Effects**

- Vasodilatory-related (more with dihydropyridines): dizziness, flushing, headache, peripheral edema
- Gingival hyperplasia
- Mood swings & fatigue
- Verapamil causes constipation (7%) and contraindicated in CHF
Oral and parenteral vasodilators

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name(s)</th>
<th>Doses available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine</td>
<td>Apresoline®</td>
<td>Oral: 10, 25, 50, 100mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parenteral: 20mg/mL soln</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>Nitropress®</td>
<td>Parenteral: 50mg/vial</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>Loniten®</td>
<td>Oral: 2.5, 10mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Topical (Rogaine®, etc): 2% soln</td>
</tr>
<tr>
<td>Diazoxide</td>
<td>Hyperstat® IV</td>
<td>Oral: 50mg capsule</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parenteral: 15mg/mL</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>Corlopam®</td>
<td>Parenteral: 10mg/mL soln</td>
</tr>
</tbody>
</table>

**Hydralazine**

- Well absorbed orally, short $t_{1/2}$ (1 hr), peak effect (1/2 hr to 2 hrs) & duration of action (12hr).
- Bioavailability determined by acetylator status: 16% in ‘fast’ and 35% in ‘slow’ acetylators.
- Adverse effects limit use. Reserved for refractory severe hypertension used concomitantly with diuretics and β-blockers (never as monotherapy).
- Used occasionally with isosorbide dinitrate in CHF.

*Contraindicated in CAD and > 40years*
Hydralazine

- Direct relaxation of arteries (not veins), cAMP mediated.

- Vasodilatation causes baroreceptor-mediated reflex, sympathetic stimulation $\rightarrow$ tachycardia $\rightarrow$ ↑ CO; ↑ renin release $\rightarrow$ ↑ Na$^+$ and H$_2$O retention.

- ↑CO and fluid retention cause tachyphylaxis, unless used in combination with β-blockers (↓ reflex tachycardia) and diuretics (↓ fluid retention).

Hydralazine: Adverse Effects

- Direct extension of pharmacological activity:
  - headache, nausea, flushing, dizziness, hypotension, palpitation, tachycardia, angina pectoris, MI

- Immunological reactions (unknown mechanism):
  - Serum sickness, hemolytic anemia, vasculitis, rapidly progressing glomerulonephritis
  - 10-20% incidence of reversible dose-related lupus erythematosus-like syndrome – high dose or after >6mth chronic use. (Use <200mg daily)
    - Effect > in females and ‘slow acetylators’.

Limited usefulness in hypertension
Minoxidil

- Direct relaxation of arteries (not veins).

↑blood flow to skin, skeletal muscles, GI tract, heart.

Reflex ↑CO, renal vasodilatation and ↑renin secretion.

Minoxidil

- > potency than hydralazine

Well absorbed orally, short $t_{1/2}:3–4$ hrs, duration of action: 12hr.

NEVER as monotherapy, use with β-blockers and diuretics (loop diuretic).

Reserved for refractory severe hypertension.
Minoxidil – Adverse Effects

- More dramatic ↑fluid retention than hydralazine (not ↑renin and aldosterone secretion related). ↓renal perfusion pressure and reflex stimulation of renal tubular α-receptors.
- Headache, sweating
- Hypertrichosis:
  Used topically to treat of male-pattern baldness.

Sodium nitroprusside

- Given by _iv_ continuous infusion. Onset: 30sec; peak effect: 2 mins.
- Metabolized to NO and cyanide.
  1. NO causes vasodilatation.
  2. Cyanide is poisonous, and further metabolized to thiocyanate.
- Very potent vasodilator of both arteries and veins
- Drug of choice in hypertension emergencies (BP>210/150mmHg).
Sodium nitroprusside

- Modest ↑HR and ↓myocardial O₂ demand

- Other indications:
  - Acute aortic dissection (propranolol given first to prevent reflex sympathetic activation).
  - In CHF to ↑CO
  - In acute MI to ↓myocardial O₂ demand

Sodium Nitroprusside: Adverse Effects

- Cyanide and thiocyanate poisoning:
  - Anorexia, nausea, fatigue, disorientation, toxic psychosis.
  - Closely monitor BP and plasma thiocyanate (<0.1μg/mL).
  - Antidote: Infusion of sodium thiosulphate → thiocyanate
  - ↑risk of poisoning in impaired renal function

- Worsens arterial hypoxemia in COPD

- Abrupt cessation after short-term use causes rebound HTN.
## Prescribed Antihypertensive Drugs in Trinidad (n=442)

<table>
<thead>
<tr>
<th>Drug Class/Generic Drug Name</th>
<th>All HTN N (%)</th>
<th>HTN alone N (%)</th>
<th>HTN with DM N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE Inhibitors (ACEI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>281 (63.6)</td>
<td>113 (58.9)</td>
<td>168 (72.7)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>247</td>
<td>95</td>
<td>152</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Captopril</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>β-blockers (BB)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>129 (29.2)</td>
<td>65 (33.9)</td>
<td>64 (25.6)</td>
</tr>
<tr>
<td>Propranolol</td>
<td>9</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide (bendrofluazide)</td>
<td>114 (25.8)</td>
<td>66 (34.4)</td>
<td>48 (19.2)</td>
</tr>
<tr>
<td>Triamterene</td>
<td>89</td>
<td>50</td>
<td>39</td>
</tr>
<tr>
<td>Furosamide</td>
<td>25</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td><strong>Calcium channel blockers (CCB)</strong></td>
<td>53 (12.0)</td>
<td>23 (12.0)</td>
<td>30 (12.0)</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>45</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Verapamil</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>α-blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prazosin</td>
<td>3 (0.7)</td>
<td>1 (0.5)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Angiotensin receptor blockers (ARB)</strong></td>
<td>10 (2.3)</td>
<td>5 (2.6)</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>Valsartan</td>
<td>9</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Prosartan</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Other drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyldopa</td>
<td>27 (6.1)</td>
<td>18 (9.4)</td>
<td>9 (3.6)</td>
</tr>
<tr>
<td>Reserpine</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

## Antihypertensive drug therapy in Trinidadian patients with complete accessible drug records (n=442)

<table>
<thead>
<tr>
<th>Antihypertensive drug therapy</th>
<th>All HTN patients N (%)</th>
<th>HTN alone N (%)</th>
<th>HTN with DM N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No drug therapy</td>
<td>26 (5.9)</td>
<td>8 (4.2)</td>
<td>18 (7.2)</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>242 (54.8)</td>
<td>86 (44.8)</td>
<td>156 (62.4)</td>
</tr>
<tr>
<td>Dual drug therapy</td>
<td>121 (27.3)</td>
<td>62 (32.3)</td>
<td>59 (23.6)</td>
</tr>
<tr>
<td>Triple drug therapy</td>
<td>45 (10.2)</td>
<td>30 (15.6)</td>
<td>15 (6.0)</td>
</tr>
<tr>
<td>Quadruple drug therapy</td>
<td>8 (1.8)</td>
<td>6 (3.1)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>442</td>
<td>192</td>
<td>250</td>
</tr>
</tbody>
</table>
↑ sympathetic activity
  ↓ BP
  ↓ Renal flow  → ↑ renin → ↑ Angiotensin II
  ↓ GFR  → ↑ Aldosterone
  → ↑ Na⁺, H₂O retention → ↑ Blood volume

↑ β₁ receptor cardiac activation
↑ α₁ receptor smooth muscle activation

↓ BP
↓ Renal flow  → ↑ renin → ↑ Angiotensin II
↓ GFR  → ↑ Aldosterone
↓ GFR  → ↑ Na⁺, H₂O retention → ↑ Blood volume

β-blockers
α₁-blockers
Ca²⁺-channel blockers
Vasodilators
ACE inhibitors
AgII receptor blockers
Diuretics

↑ CO
↑ TPR
↑ BP