Hypertension and Antihypertensive Agents

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Blood Pressure Classification – JNC VII

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP mmHg</th>
<th>DBP mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>120–139</td>
<td>80–89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>&gt;160</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

Antihypertensive Agents (JNC VII, 2003)

1. Diuretics eg. hydrochlorothiazide
2. Renin / AgII (ACEI, ARBs) eg. captopril, losartan
3. Beta-antagonists eg. propranolol
4. Calcium-antagonists eg. nifedipine, verapamil
5. Alpha-antagonists eg. prazosin
6. Potassium sparing eg. spironolactone
7. Vasodilators eg. hydralazine, nitroprusside
8. Central acting alpha2-agonists: eg. clonidine, a-methyl dopa
9. Inhibit/reduce NE release eg. guanethidine, reserpine
10. Ganglionic blockers eg. methyldopa

Antihypertensive Usage (ACC, 2001)

For untreated patients patients with BP of 140-159/90-99 mmHg and no other risk factors, indicate which class(es) of medications you would use:

<table>
<thead>
<tr>
<th>% Selecting each class</th>
<th>Cardiologist</th>
<th>GP/FP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor / ARB</td>
<td>71.6</td>
<td>57.5</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>57.9</td>
<td>50.2</td>
</tr>
<tr>
<td>Ca-blocker</td>
<td>51.5</td>
<td>35.6</td>
</tr>
<tr>
<td>Diuretics</td>
<td>48.8</td>
<td>54.5</td>
</tr>
<tr>
<td>Alpha-blocker</td>
<td>16.4</td>
<td>17.2</td>
</tr>
<tr>
<td>Other class</td>
<td>4.4</td>
<td>5.1</td>
</tr>
<tr>
<td>None (life-style)</td>
<td>8.4</td>
<td>15.3</td>
</tr>
</tbody>
</table>
Diuretics
Frontline class (1st among equals)
- ↓ BP by body depletion of Na⁺ and reducing blood volume (BV)
- High clinical value as antihypertensive
- Effective in older patients (less β-blockers, ACEI)
- Less effective in lean individuals
- Used also in treatment of Congestive Heart Failure
- Often used in combination with β-blockers or vasodilators
- Effective when GFR > 30ml/min (normal: 125ml/min)

Diuretics - Mechanism of action
Initial:
- body Na⁺ → ↓ BV → ↓ CO → ↓BP  (↑TPR, reflex)
Chronic:
- CO unchanged, ↓ TPR, ↓ NE → ↓[Ca++]i → ↓ vascular tone
Direct vasodilation effect:
- probably by opening K⁺ channels

Thiazides:
- eg. hydrochlorothiazide
- act on early distal tubule
- inhibit Na⁺ reabsorption

Loop Diuretics:
- eg. furosemide
- act on loop of Henle
- most potent

Diuretics - Adverse effects
(Thiazide & Loop)
- potassium depletion → hypokalemia: hazardous in persons taking digitalis → arrhythmia
- magnesium depletion → arrhythmia
- photosensitivity
- impair glucose tolerance → diabetes
- increase serum lipids (usually returns to normal)
- increase serum uric acid concentration → gout

Potassium Sparing Diuretic Agents
- eg. Spironolactone
- aldosterone antagonist
- act on late distal tubule (collecting duct) to inhibit Na⁺ reabsorption and K⁺ secretion
- weak action
- hyperkalemia
- commonly used in combination therapy with other antihypertensive agents

Centrally acting sympatholytic agents
Useful class
- Act on central α₂-receptors → ↓ sympathetic outflow
- Good clinical value as antihypertensives.
Clonidine, Guanfacine
 α₂-Methyldopa (converted to α₂-methyl-NE)
- do not interfere with exercise tolerance
- no metabolic effects
Adverse effects:
- sedation, mental depression, lactation, dry mouth
- withdrawal effect: rebound HT  (can be very serious)
Ganglion-Blocking Agents
- block ganglionic nicotinic receptors (SNS, PNS)
- first effective antihypertensive class
- currently not used for chronic HT

Adverse effects (significant):
- Sympathoplegia:
  - excessive orthostatic hypotension, sexual dysfunction
- Parasympathoplegia:
  - constipation, ↓ urine, blurred vision, dry mouth
- Trimethaphan
  - i.v. injection, rapid, short half life (precise titration)
  - hypertensive crisis (CNS-mediated), controlled hypotension during surgery
- Mecamylamine: effective orally

Neurons of the ANS

Postural (Orthostatic) Hypotension
- Venous return falls
- Blood pressure falls

BP (mmHg)

<table>
<thead>
<tr>
<th>95</th>
<th>100</th>
<th>95</th>
</tr>
</thead>
<tbody>
<tr>
<td>195</td>
<td>100</td>
<td>105</td>
</tr>
</tbody>
</table>

no reflex reflex

- Sympathetic activity increases
- Constriction of arteries (↑ TPR)
- Increase in heart rate
- Reflex mediated

Adrenergic Neuron-Blocking Agents
- Guanethidine (last resort), bretylium
  - inhibits release of NE from nerve terminals
  - gradual depletion of NE stores
  - neuronal uptake (uptake 1) is essential for action
  - tricyclic antidepressants, cocaine decrease effectiveness
- Reserpine (last resort)
  - inhibit uptake of NE into storage vesicle (also DA, 5-HT)
  - leads to depletion of transmitter stores (peripheral & CNS action)

Adverse effects:
- sedimentation, mental depression, Parkinsonism syndrome
- increases gastric acid secretion → ulcer

Reserpine
- Clinical value as antihypertensive is low

Adverse effects:
- marked postural hypotension
- diarrhea, impaired ejaculation

Alpha-Adrenoceptor Antagonists
- Use low, but constant
  - Phenoxybenzamine (irreversible α1-receptor blocker)
    - reflex tachycardia effect
    - therapeutic value in pheochromocytoma, HT crisis
  - Prazosin (selective α1-receptor blocker)
    - selective alpha1-receptor blocker in arterioles and venules (dilates both resistance and capacitance vessels)
    - does not produce reflex tachycardia
    - also used for benign prostate hypertrophy
  - Phentolamine (non-selective α-receptor blocker)
    - reflex tachycardia effect
    - diagnostic and therapeutic value in pheochromocytoma

Adverse effects:
- postural hypotension
- salt and fluid retention
- beneficiary effect on plasma lipids
**Benign Prostate Hypertrophy (BPH)**

Enlarged prostrate leads to difficulty in urination

Alpha-receptor blocker (ie Prazosin) cause prostrate relaxation

Relaxed prostrate improves urination

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**Beta-Adrenoceptor Antagonists**

Frontline as antihypertensive agents

Mechanisms of action:
- Central effect: inhibition of central sympathetic tone
  - BUT: beta-blockers (like Nadolol, Sotalol don’t cross CNS)
- Inhibition of renin secretion (beta1-receptors)
  - BUT: beta-blockers ↓ BP when plasma renin activity low
  - beta-blockers (like Pindolol) don’t ↓ plasma renin activity
- Effect on cardiac beta1-receptors: ↓ HR → ↓ CO → ↓ BP
  - BUT: with continued treatment CO unchanged, ↓ TPR → ↓ BP

Other Clinical Uses:
- Angina
- Congestive heart failure (CHF)
- Glaucous (Timolol)
- Panic stress
- Migraine
- Hyperthyroidism (propranolol)
- Tremor

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**Beta-Adrenergic Receptor Antagonists**

Clinically a more useful class of drugs than α-adrenoceptor antagonists.

β-Adrenoceptor antagonists vary in respect to:

- Selectivity: Relative affinity for beta1- and beta2-adrenoceptors
  - propranolol (β1, β2) vs atenolol (β1)
- Intrinsic β-activity (ISA): also act as agonists at β-adrenoceptors, propranolol (no) vs pindolol (yes)
- Local anaesthetic activity (LA-action): their ability to stabilize excitable membranes
  - propranolol (yes) vs atenolol (no)
- Lipid solubility: propranolol (high) vs atenolol (low)

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**Propranolol - Hypertension**

- Non-selective
- No partial agonist (no ISA)
- Membrane stabilization (no LA-action)
- Less effective in smokers, Afro-Americans, or elderly

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- Non-selective
- No partial agonist (no ISA)
- Membrane stabilization (no LA-action)

- Less effective in smokers, Afro-Americans, or elderly

---

**Beta-Adrenoceptor Blocking Agents (-olol) (A-M β1-selective)**

Properties of several beta-receptor blocking drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Selectivity</th>
<th>Partial Agonist Activity</th>
<th>Local Anaesthetic Activity</th>
<th>Lipid Solubility</th>
<th>Elimination Half-Life</th>
<th>Atenolol Activity</th>
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</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>S</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>2-4 hours</td>
<td>70</td>
</tr>
<tr>
<td>Inderal</td>
<td>S</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>6-9 hours</td>
<td>80</td>
</tr>
<tr>
<td>Betaxol</td>
<td>S</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>1-3 hours</td>
<td>70</td>
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<tr>
<td>Carvedilol</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
<td>3-5 hours</td>
<td>90</td>
</tr>
<tr>
<td>Labetalol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>5-6 hours</td>
<td>70</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>2-4 hours</td>
<td>80</td>
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<tr>
<td>Nadolol</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
<td>Very low</td>
<td>4-6 hours</td>
<td>90</td>
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<tr>
<td>Propranolol</td>
<td>Non</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
<td>3-4 hours</td>
<td>90</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Non</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
<td>3-4 hours</td>
<td>90</td>
</tr>
<tr>
<td>Tenormol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
<td>4-5 hours</td>
<td>50</td>
</tr>
</tbody>
</table>

*Partial agonist effects at β-receptors. Labetalol also blocks α-adrenergic blockade. ISA activity is dose-dependent.

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**Mixed Alpha- and β-Receptor Blockers**

- **Labetalol**
  - Hypertensive crisis, chronic hypertension, CHF
  - Competitive antagonist at both α- & β-ARs
  - β1 = β2 activity > α-activity (3:1)
  - HR & CO unchanged; ↓ TPR → ↓ BP
  - Some intrinsic β-receptor activity (ISA)

- **Carvedilol**
  - Newest agent
  - Chronic hypertension, Congestive heart failure (CHF)
**β-Blockers: Untoward Effects, Contraindications**

- **Supersensitivity:**
  Rebound effect with β-blockers, less with β-blockers with partial agonist activity (ie. pindolol).
  Gradual withdrawal

- **Asthma:**
  Blockade of pulmonary β₂-receptors will increase airway resistance (bronchospasm)

- **Diabetes:**
  Compensatory hyperglycemic effect of EPI in insulin-induced hypoglycemia is removed by block of β₂-ARs in liver. β₁-selective agents preferred

- **CNS:** nightmares, mental depression, insomnia

**β-Blockers: Heart Failure**

- **Old view (before 2002)**
  Contraindicated: β-blockers can precipitate latent heart failure by removing compensatory increase in sympathetic effects on heart. Pindolol has less of this effect due to intrinsic activity.

- **New view**
  May be used for CHF with caution. Not suitable in unstable heart failure, or evidence of bronchospasm, fluid overload, significant bradycardia (decreased cardiac reserve) or depression.

**Beta-Blockers in CHF: 2002 Guideline**

- Reversible heart failure
- Asymptomatic
- History of myocardial infarction or LVF ≤ 40%
- β-blocker therapy and titration
- Stable heart failure
- Any of:
  - Current symptoms and signs of heart failure
  - Evidence of fluid overload
  - Hypertension
  - Declining renal function
  - Recent (within 6 months) exacerbation or intolerance to therapy

**Beta-Blockers - Mechanism of Action**

- β-Adrenergic blockers:
  - Activation of β₂-adrenergic receptors on heart
  - Peripheral resistance

**Actions of Vasodilators**

- **Ca²⁺ Antagonists**
  - Verapamil
  - Nifedipine

- **Open K⁺ Channels**
  - Minoxidil
  - Diazoxide

- **Nitric Oxide (NO) Vasodilators**
  - Hydralazine
  - Nitroprusside
  - Nitrates

**Vasodilators**

- Relax smooth muscle of arterioles → ↓ TPR
- High clinical value (in combinations and hypertensive emergencies)

**Hydralazine**

- EDRF / Nitric oxide (NO) / cGMP involvement
- Dilate arterioles but not veins
- ↓ TPR → ↓ BP → reflex tachycardia

**Adverse effects:**

- Reflectory sympathetic activation
- Headache, nausea, sweating, flushing
- Palpitations, ↑ HR → angina
- Lupus reaction (mainly in slow acetylators)
Vasodilators - Minoxidil

Minoxidil (Rogaine)
- opens K⁺-channels in smooth muscle membranes
- stabilization of membrane at its resting potential, contraction less likely
- dilates arterioles but not veins

Adverse effects:
- reflex sympathetic stimulation
- fluid retention (value in combination therapy)
- hypertrichosis (topical application as Rogaine)

Vasodilators – Sodium Nitroprusside

Sodium Nitroprusside
- activation of guanylyl cyclase (direct and/or via release of NO
- intracellular ↑ cGMP → relaxation of vascular smooth muscle
- dilates both arterial (↓ TPR) and venous vessels
- venous return to the heart is decreased, reflex tachycardia
- hypertensive emergency, acute CHF
- i.v. administration, never oral → ↑ toxicity

Adverse effects:
- cyanide liberation → cyanide toxicity
- thiocyanate elimination by the kidney (high dose / long infusion, insufficient sulfur donor, defect in cyanide metabolism)
- metabolic acidosis, arrhythmias, severe hypotension
- methemoglobinemia (non-reversible O₂ binding)

Vasodilators - Diazoxide

Diazoxide
- opens K⁺-channels - stabilizes membrane potential
- dilates arteriolar vessels
- i.v. administration
- ↓ TPR → reflex ↑ HR → ↑ CO
- inhibits insulin release (via opening K⁺-channels on beta cell membrane)
- similar structure as thiazide diuretics but no diuretic effect

Calcium Channel Blockers

Frontline class
- inhibition of calcium influx into arterial smooth muscle cells
- dilate arterioles → ↓ TPR → ↓ BP
- different effect on the heart and vessels
- contraindicated in Congestive heart failure (CHF)

Nifedpine:
- mainly arteriole vasodilation, little direct cardiac effect
- may cause reflex tachycardia, flushing, peripheral edema

Verapamil:
- some cardiac slowing, constipation
- caution in digitalized patients (↑ digoxin levels)

Diltiazem:
- similar to Verapamil / Nifedpine (less)
- both cardiac and vascular actions

Calcium blockers - Gingival Hyperplasia

- Calcium blockers – especially nifedipine (10%)
- Phenytoin (Dilantin) – for seizures (40%)
- Cyclosporine – immunosuppressant (30%)

Action of Vasodilators
Renin-Angiotensin-Aldosterone System

Frontline class of antihypertensive agents
- inhibit action (ARB) or production of angiotensin II (ACEI)
- AgII is a potent vasoconstrictor peptide
- decrease aldosterone production
- less effective in elderly, Afro-Americans

ACE is a peptidyl dipeptidase:
- converts AgI to active AgII (major effect)
- degrades bradykinin (a potent vasodilator)

Angiotensin-Converting Enzyme (ACE) Inhibitors

Captopril: - orally active
Enalapril: - for i.v. use, hypertensive emergency
Benazepril, Fosinopril, Ramipril: - longer acting agents
  ↓ TPR, CO unchanged, HR unchanged
  - no reflex ↑ HR, probably due to resetting (↓) of baroreceptor reflex sensitivity
  - improves intrarenal hemodynamics (good for diabetes)
  - reverse cardiac hypertrophy seen in HT
  - less effective with age and in Afro-Americans
  - need to take before or after meals

Saralazin, Lorsarton (ARBs, receptor antagonists)
- competitive inhibitor of AgII at its receptor
- has a weak agonist activity (depends on circulating AgII level)
- diagnostic value (AgII dependency of HT)

Actions of Angiotension Converting Enzyme

Angiotensinogen → Angiotensin I → Angiotensin II

Vasoconstriction
- Increased TPR
- Increased BP
- Aldosterone secretion
- Increased NA & H₂O retention
- Decreased TPR
- Decrease BP

ACE Inhibitors & ARBs - Adverse effects

- severe hypotension in hypovolemic patients, bilateral renal artery stenosis
- hyperkalemia ([K⁺])
- dry cough (ACEI), dry mouth, skin rushes, glossitis
- altered sense of taste due to loss of Zinc (10-20%)
- tetrogenic, contraindicated during the second and third trimester of pregnancy
- drug interactions with potassium-sparing diuretics, NSAID

ACEI - Glossitis

- Less than 5%
- Dry mouth
- Glossitis
- Oral ulceration (Stevens-Johnson Syndrome)
- Oral bleeding

Treatment of Hypertension (> 139/89mmHg)

General considerations

Secondary HT (10%)
- can be cured by surgical procedures (early diagnosis of cause)
- renal artery stenosis, pheochromocytoma

Primary (essential) HT (90%)
- is a lifelong disease, long-term control & treatment
- HT often insidious, causes no symptoms
- conversely treatment can produce even serious

Adverse effects:
- patients compliance is very important
- treat the patient and not 'just' their BP (quality of life)
Patients whose Hypertension is Controlled

<table>
<thead>
<tr>
<th>Country</th>
<th>Controlled &lt;140/90 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>27%</td>
</tr>
<tr>
<td>Canada</td>
<td>16%</td>
</tr>
<tr>
<td>England</td>
<td>9%</td>
</tr>
<tr>
<td>France</td>
<td>24%</td>
</tr>
</tbody>
</table>

Hypertension Is Largely Uncontrolled Across Ethnic Groups

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Present but patient unaware</th>
<th>Acknowledged, untreated</th>
<th>Treated, uncontrolled</th>
<th>Treated, controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whites (n=122.8 million)</td>
<td>31%</td>
<td>27%</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>African Americans (n=5.7 million)</td>
<td>17%</td>
<td>19%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Mexican Americans (n=1.3 million)</td>
<td>24%</td>
<td>24%</td>
<td>15%</td>
<td></td>
</tr>
</tbody>
</table>

Treatment strategy

Initial step: Nonpharmacological
- sodium intake, weight loss, physical activity, alcohol, stress,
- overview of medication, other risk factors

IF NOT ENOUGH OR INITIALLY HIGHER STAGE OF HT

Drug therapy:
- start with drug therapy (frontline agents, thiazide 1st)
- choose the proper medication for lifestyle
- β-blockers efficacy may decrease as age increases
- β-blockers are less effective in smokers
- blacks respond less to β-blockers and ACE inhibitors
- β-blockers and ACE inhibitors better in ↑ plasma renin
- use long-lasting drugs (↑ compliance)

Start with monotherapy:
- if necessary add second, or third agent (from different class)

Good Combotherapy: vasodilator with either β-blocker or diuretic

Lifestyle Modification

<table>
<thead>
<tr>
<th>Modification</th>
<th>Approximate SBP reduction (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>5-20 mmHg/10 kg weight loss</td>
</tr>
<tr>
<td>Adopt DASH eating plan</td>
<td>8-14 mmHg</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>2-8 mmHg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>4-9 mmHg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>2-4 mmHg</td>
</tr>
</tbody>
</table>

Treatment strategy

Initial step: Nonpharmacological
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- overview of medication, other risk factors

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Good Combotherapy: vasodilator (CCB) with either β-blocker or diuretic

Antihypertensive Market

U.S. ANTHYPERTENSIVE MARKET

<table>
<thead>
<tr>
<th>Year</th>
<th>Diuretics</th>
<th>Beta Blockers</th>
<th>ACE Inhibitors</th>
<th>Calcium Channel Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>40</td>
<td>20</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>2001</td>
<td>42</td>
<td>22</td>
<td>12</td>
<td>12</td>
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<tr>
<td>2002</td>
<td>44</td>
<td>24</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>2003</td>
<td>46</td>
<td>26</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>2004</td>
<td>48</td>
<td>28</td>
<td>18</td>
<td>18</td>
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<td>2005</td>
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<td>2006</td>
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<td>32</td>
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<td>2007</td>
<td>54</td>
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<td>2008</td>
<td>56</td>
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<td>2010</td>
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<td>2011</td>
<td>62</td>
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<td>2012</td>
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<td>2014</td>
<td>68</td>
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<tr>
<td>2015</td>
<td>70</td>
<td>50</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

Total Rx's

- Diuretics
- Beta Blockers
- ACE Inhibitors
- Calcium Channel Blockers

Total Rx's in U.S.

- 1990
- 1992
- 1994
- 1996
- 1998
- 2000
- 2002
- 2004
- 2006
- 2008
- 2010
- 2012
- 2014
- 2016
- 2018

Patients whose Hypertension is Controlled

<table>
<thead>
<tr>
<th>Country</th>
<th>Controlled &lt;140/90 mmHg</th>
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</thead>
<tbody>
<tr>
<td>USA</td>
<td>27%</td>
</tr>
<tr>
<td>Canada</td>
<td>16%</td>
</tr>
<tr>
<td>England</td>
<td>9%</td>
</tr>
<tr>
<td>France</td>
<td>24%</td>
</tr>
</tbody>
</table>
Hypertension Treatment Chart

US mean cost per prescription

White coat effect

JAMA, 291: 1850-56, 2004

Am J Hypertension 2003; 16: 484-497