Although data linking increased blood pressure to premature death were long available, the prevailing medical opinion well into the 1950s was that *lowering of elevated blood pressure was detrimental because it would impair perfusion of vital organs, and thereby increase the risk of cardiovascular disease*. Further, elevated blood pressure was viewed as *essential* to perfusion of vital organs *(i.e., “essential hypertension”)*.
Early Therapeutic Approaches

1. Kemper W (1948) – rice diet
2. Smithwick RH (1952) – bilateral lumbodorsal sympathectomy and splanchnicectomy
3. Wilkins RW (1952, 1953) – drug therapies

Early Studies Demonstrating Benefits of Antihypertensive Therapy

• Dustan HP and coworkers at the Cleveland Clinic (1958) reported the effectiveness of long-term treatment of malignant hypertension.

• Freis E and coworkers (1967 and 1970) showed impressive reduction in cardiovascular events among patients with pretreatment DBP of 115 to 129 mm Hg and later among those with DBP of 90-114 mm Hg.
Results of Placebo-Controlled Studies

- Incidence of stroke reduced by 35 to 40%
- Incidence of coronary events reduced by 20 to 25%
- Incidence of heart failure reduced by >50%

Historical Trends in HTN*

National Health and Nutrition Examination Survey

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Awareness</td>
<td>51%</td>
<td>73%</td>
<td>68%</td>
<td>70%</td>
</tr>
<tr>
<td>Treatment</td>
<td>31%</td>
<td>55%</td>
<td>54%</td>
<td>59%</td>
</tr>
<tr>
<td>Control</td>
<td>10%</td>
<td>29%</td>
<td>27%</td>
<td>34%</td>
</tr>
</tbody>
</table>

*Hypertension = SBP >140 mmHg and DBP >90 mmHg

http://hin.nhlbi.nih.gov/nhbpep_slds/menu.htm
Rates of Awareness, Treatment, and Control of High Blood Pressure in the USA, 1976-2004

<table>
<thead>
<tr>
<th></th>
<th>Awareness</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHANES II 1976-89</td>
<td>51</td>
<td>31</td>
<td>10</td>
</tr>
<tr>
<td>NHANES III (phase 1) 1988-91</td>
<td>73</td>
<td>55</td>
<td>29</td>
</tr>
<tr>
<td>NHANES III (phase 2) 1991-94</td>
<td>68</td>
<td>54</td>
<td>27</td>
</tr>
<tr>
<td>NHANES 1999-2004</td>
<td>72</td>
<td>61</td>
<td>35</td>
</tr>
</tbody>
</table>


Changes in the Prevalence and Control of Hypertension in the USA, 1998-2004

<table>
<thead>
<tr>
<th></th>
<th>Controlled</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-1994</td>
<td>50</td>
<td>13</td>
</tr>
<tr>
<td>1999-2004</td>
<td>65</td>
<td>23</td>
</tr>
</tbody>
</table>

Reasons for Continued Rise in Uncontrolled Hypertension

1. Failure to adopt a healthy lifestyle
   - Lack of exercise
   - Increased salt/low potassium intake
   - Increased consumption of calories and saturated fat → obesity
   - Excessive alcohol intake
2. Use of illicit drugs or over-the-counter medications
3. Increased prevalence of co-existing disease
4. Poor management of isolated systolic hypertension
5. Non-adherence to treatment – estimated rates are 51% to 79% depending on the number of daily doses prescribed.

In large part, the low control rate of hypertension can be attributed to poor management of isolated systolic hypertension in the elderly.

Increase in the Prevalence of Hypertension

Increased number of persons at risk for the development of established hypertension

1. Large numbers (30%) of the U.S. adult population have prehypertension (BP 120-139/80-89 mm Hg)
2. Aging of the population – approximately 90% of persons who have normal BP at 55 or 65 years of age become hypertensive in the subsequent 20 years
3. Increased prevalence of obesity, diabetes mellitus and renal disease
Rates of Progression from Prehypertension to Hypertension over a 4-Year Period

- For persons age 35 to 64 years – 37%
- For persons 65 year and older – 50%


Risk Factors for Hypertension

- Genetic predisposition or family history
- Black race
- Diagnosis of prehypertension
- Increasing age
- Obesity
- High sodium-low potassium intake
- Excessive alcohol intake
- Low socioeconomic status
- Sleep apnea
- Use of certain illegal drugs or over-the-counter medications

HYPERTENSION: Definition and Classification

Every Life Deserves World Class Care

<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>and &lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120–139</td>
<td>or 80–89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140–159</td>
<td>or 90–99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>≥160</td>
<td>or ≥100</td>
</tr>
</tbody>
</table>

Another View……
ASH Position Paper 2005

“This paradigm expands on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) definition and classification of hypertension by classifying individuals by blood pressure (BP) level or cardiovascular status; however, priority is given to cardiovascular status; cardiovascular disease (CVD) designation is determined by the constellation of risk factors, early disease markers, and target organ disease”

(From Clin Hypertens. 2005;7:505–512)
Developing Risk Scores

• Comprehensive vascular evaluation of hypertensive patients to accurately stratify and manage based on risks

• Framingham Risk Score:
  – Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)

• Rasmussen Score

Rasmussen Score

1. Small-artery elasticity using pulsewave analysis
2. Large-artery elasticity using pulsewave analysis
3. Blood pressure at rest
4. Blood pressure after three minutes of exercise
5. Optic fundus photos taken with a digital camera
6. Microalbuminuria
7. Carotid artery ultrasound to measure artery wall thickness
8. Electrocardiogram
9. Left ventricular ultrasound to measure heart size
Rasmussen Center for Cardiovascular Disease Prevention

- 0 (normal)
- 1 (borderline)
- 2 (abnormal)

Patients then receive a composite score known as their Rasmussen score.

A score of 6 or higher is considered cause for concern.

WHICH BP DO WE USE FOR STAGING AND TREATMENT OF HYPERTENSION?

- Office BP
  - Nurse, medical assistant, doctor, machinery (e.g., BP Tru)
- Home BP (self-monitoring)
- 24-hr ambulatory blood pressure monitoring (ABPM)
LABELLING THE PATIENT AS "HYPERTENSIVE"

- Confirm elevated office BP readings
- BP consistently >135-140 / 85-90 at home
- 24-hr ABPM
  - Average awake BP >135/85
  - Average asleep BP >120/75

BP MEASUREMENT IN THE OFFICE

1. Technique of BP measurement:
   - 5 minutes of rest, no conversation, seated comfortably
   - Arm should at the level of the heart
   - No tobacco or caffeine intake in the preceding 30 minutes
2. Two seated readings should be obtained and averaged
3. Two upright readings (after 1 minute of quiet standing) should be obtained and averaged.
Automated Office BP Device

- White coat effect
- Work in progress

BpTRU: Rationale

- Oscillometric device
- Tested extensively
- Independently validated device
- Automatically zeroes with each inflation
- Average of 6 readings
- Integration to EMR
WHICH BP SHOULD WE BELIEVE?


Reduction of WCE in Clinical Practice

INDICATIONS FOR ABPM

1. Evaluation of disparate office and home BP readings
   a. Elevated office readings – “office” or “white coat” hypertension
   b. Low or normal office readings with target organ damage
2. Assessment of borderline or labile hypertension
3. Assessment of efficacy of therapy
4. Evaluation of episodic hypertension or orthostatic hypotension
5. Clinical pharmacology studies of new drugs/research
ASSOCIATION BETWEEN OFFICE BP AND 24-HR ABPM

<table>
<thead>
<tr>
<th>24-Hr Ambulatory BP</th>
<th>24-Hr Ambulatory BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>controlled</td>
<td>NOT controlled</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Office BP controlled</th>
<th>Normotension</th>
<th>Masked hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office BP not controlled</td>
<td>White coat hypertension</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

Office BP not controlled is highlighted.
### FEATURES OF ATYPICAL HYPERTENSION

1. Age of onset:  
   - <20; >50 yrs
2. Level of BP:  
   - >180/110 mmHg
3. Target organ damage
   a. Fundi - Grade II or worse
   b. Serum creatinine >1.5 mg/dL
   c. Cardiomegaly or LVH
4. Presence of features suggesting secondary causes
   a. Unprovoked hypokalemia
   b. Abdominal bruit
   c. Variable BP with tachycardia, sweating, tremor
   d. Family history of renal disease, proteinuria
5. Poor response to appropriate drug regimen

### Causes of Secondary Hypertension

1. Renovascular hypertension
2. Renal parenchymal disease
3. Primary aldosteronism
4. Pheochromocytoma
5. Cushing’s syndrome
6. Coarctation of the aorta
7. Liddle’s Syndrome
8. Obstructive sleep apnea
9. Illicit drug abuse
10. Obesity
JNV-VII DEFINITION OF RESISTANT HYPERTENSION

• “Resistant hypertension is the failure to reach goal BP in patients who are adhering to full doses of an appropriate 3-drug regimen that includes a diuretic.

• Treating SBP and DBP to targets that are <140/90 mm Hg is associated with a decrease in CVD complications. In patients with hypertension and diabetes or renal disease, the BP goal is 130/80 mm Hg.”

POSSIBLE CAUSES OF RESISTANT HYPERTENSION

• Patient resistance
• Physician resistance
  — insufficient dosage
  — infrequent administration
  — irrational combinations
  — inadequate physician education
  — lack of physician motivation
• Drug interactions
• Excessive salt intake
• Office hypertension
• Secondary causes of hypertension
• True drug-resistant hypertension
Early Therapeutic Approaches

1. Kemper W (1948) – rice diet
2. Smithwick RH (1952) – bilateral lumbodorsal sympathectomy and splanchnicectomy
3. Wilkins RW (1952, 1953) – drug therapies
## Advances in the Drug Treatment of Hypertension

<table>
<thead>
<tr>
<th>1950s</th>
<th>1970s</th>
<th>1980s</th>
<th>1990s</th>
<th>2000s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Rauwolfia serpentina</em></td>
<td><em>α1-Adrenergic–receptor antagonists</em></td>
<td><em>Calcium antagonists</em></td>
<td><em>Renin inhibitors</em></td>
</tr>
<tr>
<td></td>
<td>Ganglionic blockers</td>
<td>Angiotensin-converting–enzyme inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Veratrum alkaloids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydralazine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Guanethidine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Thiazide diuretics</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1960s</td>
<td><em>α2-Adrenergic–receptor agonists</em></td>
<td></td>
<td><em>Angiotensin-receptor blockers</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spironolactone</td>
<td></td>
<td>Endothelin-receptor antagonist*</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>β-Adrenergic–receptor antagonists</em></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Evolving Approaches to Treatment

- Lifestyle modifications
- Drugs
- New treatment algorithm
### Most Useful Antihypertensive Drug Classes

1. Thiazide-type diuretics
2. β-adrenergic receptor blockers
3. ACE inhibitors
4. Calcium-channel blockers
5. Angiotensin receptor blockers

### Lifestyle Modification to Prevent and Manage Hypertension

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Approximate SBP reduction (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Maintain normal body weight (body mass index 18.4-24.9 kg/m²)</td>
<td>5-20 mm Hg/10 kg weight loss</td>
</tr>
<tr>
<td>Adopt DASH eating plan</td>
<td>Diet rich in fruits, vegetables, and low-fat dairy products with ↓ content of saturated &amp; total fat</td>
<td>8-14 mm Hg</td>
</tr>
<tr>
<td>Dietary sodium restriction</td>
<td>Reduce dietary sodium intake to ≤100 mmol/d</td>
<td>2-8 mm Hg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Engage in regular aerobic physical activity such as brisk walking (at least 30 min/day, most days of the week)</td>
<td>4-9 mm Hg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>Limit consumption to no more than 2 drinks (1 oz or 30 ml ethanol; e.g., 24 oz beer, 10 oz wine, or 2 oz of 80-proof whiskey) per d in most men and to no more than 1 drink per day in women &amp; lighter weight persons</td>
<td>2-4 mm Hg</td>
</tr>
</tbody>
</table>
Effects of low-sodium DASH diet on systolic blood pressure with increasing age

![Graph showing the effect of low-sodium DASH diet on systolic blood pressure with increasing age.]


---

JNC 7 Algorithm for Treatment of Hypertension

**Lifestyle Modifications**

- Not at Goal Blood Pressure (<140/90 mmHg)
  - (<130/80 mmHg for those with diabetes or chronic kidney disease)

**Initial Drug Choices**

- **Without Compelling Indications**
  - Stage 1 Hypertension (SBP 140–159 or DBP 90–99 mmHg)
    - Thiazide-type diuretics for most.
    - May consider ACEI, ARB, BB, CCB, or combination.
  - Stage 2 Hypertension (SBP ≥160 or DBP ≥100 mmHg)
    - 2-drug combination for most (usually thiazide-type diuretic and ACEI, ARB, or BB, or CCB)

- **With Compelling Indications**
  - Drug(s) for the compelling indications
  - Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.

**Optimize dosages or add additional drugs until goal blood pressure is achieved. Consider consultation with hypertension specialist.**
Stage I Hypertension
(BP 140-159/90-99 mm Hg)

Step 1
Single drug regimen:
ACE inhibitor, ARB, CCB, diuretic

Step 2
Add 2nd drug of a different class:
ACE inhibitor, ARB, CCB, diuretic

Step 3
Add 3rd drug of a different class:
- Assess adherence
- Optimize doses

Stage II Hypertension
(BP ≥160/100 mm Hg)

Step 1
Two-Drug Combination:
- ACEi/ARB + diuretic
- CCB + β-blocker

Step 2
Add 3rd drug of a different class:
- Assess adherence
- Assess salt intake
- Optimize doses

Step 3
Add 4th drug of a different class:
- α1 adrenergic blocker
- α2 adrenergic agonist

Step 4
Evaluate for secondary hypertension
### Drug Choices for Compelling Indications

<table>
<thead>
<tr>
<th>Co-existing Disorder</th>
<th>Drug Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-myocardial infarction</td>
<td>ACEi, β-blocker</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>ACEi, β-blocker</td>
</tr>
<tr>
<td>Heart failure</td>
<td>ACEi, β-blocker</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>ACEi, ARB, diuretic</td>
</tr>
<tr>
<td>Diabetes</td>
<td>ACEi, ARB</td>
</tr>
<tr>
<td>High coronary disease risk</td>
<td>ACEi, ARB, β-blocker, CCB, diuretic</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>CCB, diuretic</td>
</tr>
</tbody>
</table>

### Use of dihydropyridine calcium channel blockers in the management of hypertension in Eastern Asians – A scientific statement from the Asian Pacific Heart Association

- 11 trials (2 cross-over studies; 9 parallel group studies)
- N = 683 patients
- Median follow-up period <6 months
- Trials compared the effects of amlodipine vs. ACEi/ARB/β-adrenergic blocker
- Results:
  - CCB (mainly amlodipine) was more efficacious in lowering BP when compared with ACEi/ARB/β-adrenergic blocker
  - CCB might provide superior protection against stroke and coronary spasm.

Target Blood Pressure is Achievable

**BUT**

Usually Requires More Than One Drug

---

**Average Number of Antihypertensive Agents Needed Per Patient to Achieve Diastolic BP Goals**

<table>
<thead>
<tr>
<th>Study</th>
<th>Diastolic BP Goals</th>
<th>No. of BP medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS (&lt;85 mm Hg Diastolic)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>ABCD (&lt;75 mm Hg Diastolic)</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>MDRD (&lt;92 mm Hg MAP)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>HOT (&lt;80 mm Hg Diastolic)</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>AASK (&lt;92 mm Hg MAP)</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

* IT IS MORE DIFFICULT TO ACHIEVE SYSTOLIC BP GOALS.*

The most common cause of drug-resistant hypertension is the omission of diuretics in patients on multiple drug regimens.

POSSIBLE CAUSES OF RESISTANT HYPERTENSION

- Patient resistance
- Physician resistance
  - insufficient dosage
  - infrequent administration
  - irrational combinations
  - inadequate physician education
  - lack of physician motivation
- Drug interactions
- Excessive salt intake
- Office hypertension
- Secondary causes of hypertension
- True drug-resistant hypertension
GUIDELINES FOR ESTIMATING A PATIENT’S SODIUM INTAKE

<table>
<thead>
<tr>
<th>Patient’s description of salt intake</th>
<th>Approximate dietary sodium, (mEq/24 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoids salty foods and adds no salt</td>
<td>90 - 120</td>
</tr>
<tr>
<td>Adds salt in moderation</td>
<td>120 – 200</td>
</tr>
<tr>
<td>Salts food heavily, often before tasting</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>

RATIONAL TRIPLE-DRUG REGIMEN

**Diuretic + Sympathetic Inhibitor + Vasodilator**

- beta blocker
- prazosin
- clonidine
- aldomet
- labetalol
- hydralazine
- minoxidil
- ACEI
- CCB
- ARB

ACEI = ACE inhibitor  
CCB = calcium channel blocker  
ARB = angiotensin II receptor blocker
What is **NOT** Resistant Hypertension

**Hypertension with regimen of:**

- HCTZ 12.5 mg q.d.
  - Hydralazine 25 mg b.i.d.
  - Toprol XL 25 mg q.d.

**OR**

- Vasotec 5 mg q.d.
  - Lasix 40 mg q.d.
  - Procardia XL 30 mg q.d.

**AN ALGORITHM FOR THE MANAGEMENT OF RESISTANT HYPERTENSION**

Is the patient compliant?

- No

  Is the regimen adequate?

  - No

  - Yes

  Are drug-drug interactions possible?

  - No

  - Yes
AN ALGORITHM FOR THE MANAGEMENT OF RESISTANT HYPERTENSION

Are drug-drug interactions possible?
- Yes
- No

Does the patient have pseudohypertension?
- Yes
- No

Does the patient have office hypertension?
- Yes
- No

Has secondary hypertension been excluded?
- Yes
- No

Alter regimen empirically

BP controlled
- Evaluate mechanisms and alter regimen appropriately

BP NOT CONTROLLED
Four interventions repeatedly linked with improved BP

- Involvement of someone other than the physician
  —(i.e. restructuring care delivery)
- Systematically tracking and improving follow up
- Performance feedback to physicians
- Self-monitoring

*Med Care 2006 Jul 44(7): 646-57*
*Cochrane Database Sys Rev 2006; (2): CD005182*

---

**Center for BP Disorders**

**Quality Metrics 3rd Q 2008**

<table>
<thead>
<tr>
<th>Physician</th>
<th>&lt;140/90</th>
<th>&lt;130/80</th>
<th>LDL tested</th>
<th>LDL&lt;130</th>
<th>LDL&lt;100</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>68.8%</td>
<td>49.4%</td>
<td>90.5%</td>
<td>75.3%</td>
<td>51.9%</td>
<td>77</td>
</tr>
<tr>
<td>B</td>
<td>73.3%</td>
<td>45.5%</td>
<td>88.4%</td>
<td>76.2%</td>
<td>56.4%</td>
<td>101</td>
</tr>
<tr>
<td>C</td>
<td>65.6%</td>
<td>45.8%</td>
<td>90.8%</td>
<td>66.7%</td>
<td>55.2%</td>
<td>96</td>
</tr>
<tr>
<td>D</td>
<td>60.3%</td>
<td>39.7%</td>
<td>87.1%</td>
<td>77.8%</td>
<td>52.4%</td>
<td>63</td>
</tr>
<tr>
<td>E</td>
<td>56.6%</td>
<td>28.3%</td>
<td>97.8%</td>
<td>76.8%</td>
<td>57.6%</td>
<td>99</td>
</tr>
</tbody>
</table>

Inclusion criteria:
- Docs in Center for BP Disorders w/ at least 30 cases
- Pt seen at least 2x in department
- Last visit between 10/1/07-9/30/08
- ICD9 diagnosis for Htn in Epic encounter or problem list
Remarkable advances in drug therapy has provided the newfound capability for lowering blood pressure in almost every person with hypertension.

In general, studies on a given drug or drug combination have shown minimal differences in primary outcomes among the drug classes as long as equivalent reduction in blood pressure has been achieved.
Summary (III)

However, despite the enormous advances in antihypertensive drug therapy, the number of people with uncontrolled hypertension has continued to rise. Critical factors to account for this paradox include: a) failure to achieve a healthy lifestyle, b) poor management of isolated systolic hypertension, and c) high prevalence (51% to 79%) of non-adherence to drug treatment.