“Essential Hypertension”

Historical Perspectives

“The treatment of hypertension itself is a difficult and almost hopeless task, and in fact for aught we know...the hypertension may be an important compensation mechanism which should not be tampered with....”

— Paul Dudley White, 1937

Is high blood pressure a normal consequence of aging, necessary to maintain peripheral perfusion in the elderly?

“Normal BP is 100+Age..”

Franklin D Roosevelt
Died April 12 1945
BP 300/190 mmHg
Hypertension Contributes to the Development of Cardiovascular Disease

Framingham Heart Study Follow-Up of Participants Aged 35-64 years for 36 years
Hypertension Remains Common

- World population is 6 Billion
- 1 in 6 have a Mobile phone
- 1 in 6 have Hypertension
Ischemic Heart Disease Mortality Rate in Each Decade of Age

IHD mortality (floating absolute risk and 95% CI)

SBP

Usual SBP (mm Hg)

120 140 160 180

256 128 64 32 16 8 4 2 1

DBP

Usual DBP (mm Hg)

70 80 90 100 110

256 128 64 32 16 8 4 2 1

Age at risk: 80-89 y, 70-79 y, 60-69 y, 50-59 y, 40-49 y

CV complications of BP in the population (>1m Subjects)

Stable Angina (n=3949)

Myocardial Infarction (n=4486)

Ischaemic Stroke (n=937)

Cerebral Haemorrhage (n=434)

Rapsomaniki Lancet 2014; 383: 1899-1911
BP-Lowering Treatment Trialists

A = CA vs placebo; B = ACE inhibitor vs placebo; C = more intensive vs less intensive blood-pressure-lowering; D = ARB vs control; E = ACE inhibitor vs CA; F = CA vs diuretic or β-blocker; G = ACE inhibitor vs diuretic and β-blocker.

What is new about BP detection and pathophysiology?
ABPM for the Diagnosis of Hypertension

- ABPM is a better predictor of clinical outcomes than clinic BP
- ABPM is the reference standard used in clinical practice when there is uncertainty about the diagnosis
- ABPM improves the specificity and sensitivity of diagnosis versus clinic and home BP measurement
- Avoids treatment in people who are not hypertensive – as many as 25% with “white coat hypertension”
Net Resource Costs of Implementing ABPM for Diagnosis of Hypertension for England and Wales

http://guidance.nice.org.uk/CG127
MUCH: Masked Untreated Hypertension

31% of apparently controlled Patient with Hypertension (< 140/90 mmHg) in the office have elevated ABPM values during 24 hours

Banegas  Eur Heart 2014
Masked Hypertension has poor prognosis...

Angeli et al. Am J Hypertens 2010; 23:941-948
BP Is Variable: 24h Short-term

Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension

Peter M Rothwell, Sally C Howard, Eamon Dolan, Eoin O’Brien, Joanna E Dobson, Bjorn Dahlöf, Peter S Sever, Neil R Poulter

Summary

Background The mechanisms by which hypertension causes vascular events are unclear. Guidelines for diagnosis and treatment focus only on underlying mean blood pressure. We aimed to reliably establish the prognostic significance of visit-to-visit variability in blood pressure, maximum blood pressure reached, untreated episodic hypertension, and residual variability in treated patients.

Visit-to-visit variability in SBP and maximum SBP are strong predictors of stroke, independent of mean SBP.

Increased residual variability in SBP in patients with treated hypertension is associated with a high risk of vascular events.
Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis

Alastair J S Webb, Urs Fischer, Ziyah Mehta, Peter M Rothwell
What have we learnt about BP treatment?
“Treating high blood pressure is cheaper than doing nothing”
Combining antihypertensive agents is more efficacious than uptitration of monotherapy

Adding a drug from another class (on average standard doses)
Doubling dose of same drug (from standard dose to twice standard)

Incremental SBP reduction ratio of observed to expected additive effects

- **Thiazide**:
  - Adding: 1.04 (0.88–1.20)
  - Doubling: 0.19 (0.08–0.30)

- **Beta blocker**:
  - Adding: 1.00 (0.76–1.24)
  - Doubling: 0.23 (0.12–0.34)

- **ACE inhibitor**:
  - Adding: 1.16 (0.93–1.39)
  - Doubling: 0.20 (0.14–0.26)

- **Calcium channel blocker**:
  - Adding: 0.89 (0.69–1.09)
  - Doubling: 0.37 (0.29–0.45)

- **All Classes**:
  - Adding: 1.01 (0.90–1.12)
  - Doubling: 0.22 (0.19–0.25)

Most patients require combination therapy to achieve their target BP

**Patients without chronic kidney disease (achieved SBP)**
- HOT (138 mmHg)
- UKPDS (144 mmHg)
- ALLHAT (138 mmHg)
- INVEST (136 mmHg)

**Patients with chronic kidney disease (achieved SBP)**
- MDRD (132 mmHg)
- ABCD (132 mmHg)
- AASK (128 mmHg)
- IDNT (138 mmHg)
- RENAAL (141 mmHg)
19% fewer CVD events with good adherence to anti HT Rx

<table>
<thead>
<tr>
<th>Adherence Type</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>No. of CVD events</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Adherence to statins</td>
<td>17</td>
<td>1,055,920</td>
<td>96,216</td>
<td>0.85 (0.81, 0.89)</td>
</tr>
<tr>
<td>(2) Adherence to antihypertensive agents</td>
<td>13*</td>
<td>552,143</td>
<td>36,186</td>
<td>0.81 (0.76, 0.86)</td>
</tr>
<tr>
<td>ACE inhibitors/Angiotensin receptor blockers</td>
<td>4</td>
<td>68,781</td>
<td>4643</td>
<td>0.75 (0.55, 1.01)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>4</td>
<td>90,402</td>
<td>10,774</td>
<td>0.83 (0.71, 0.98)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1</td>
<td>9168</td>
<td>2249</td>
<td>0.91 (0.82, 1.01)</td>
</tr>
<tr>
<td>Multiple agents</td>
<td>7</td>
<td>443,264</td>
<td>22,714</td>
<td>0.80 (0.73, 0.89)</td>
</tr>
<tr>
<td>(3) Adherence to aspirin</td>
<td>3</td>
<td>15,253</td>
<td>2274</td>
<td>0.60 (0.31, 1.16)</td>
</tr>
<tr>
<td>(4) Adherence to any CVD medication</td>
<td>33*</td>
<td>1,615,126</td>
<td>135,627</td>
<td>0.80 (0.77, 0.84)</td>
</tr>
</tbody>
</table>

*Includes studies with a range of adherence levels.

Chowdhury et al EHJ (2013) 34, 2940–2948
NICE Guidelines 2011
Antihypertensive Drug Treatment

Aged <55yrs

Step 1
A

Step 2
A + C*

Step 3
A + C + D

Aged ≥55yrs

Step 4
A + C + D + Further Diuretic+
Consider specialist Advice

A = ACEi or ARB
C = CCB
D = Thiazide-like diuretic

C* = CCB preferred but D is an alternative in people intolerant of C or at high risk of heart failure

Further Diuretic:
Consider low dose spironolactine or higher dose thiazide
Summary of Questions

Pathway 1

Could aggressive early treatment of raised blood pressure prevent subsequent treatment resistance?

Pathway 2

Is resistant hypertension usually due to excessive Na\(^+\) retention? Is spironolactone superior to other potential add on drugs?

Pathway 3

Are K\(^+\) sparing diuretics neutral or beneficial in their effect on glucose tolerance?
PATHWAY 2: Home systolic and diastolic blood pressures comparing spironolactone with each of the other cycles

![Bar chart comparing blood pressures](chart.png)

- Baseline (n=314)
- Placebo (n=274)
- Spironolactone 25-50 mg (n=285)
- Doxazosin 4-8 mg (n=282)
- Bisoprolol 5-10 mg (n=285)

*Williams Lancet Published Online September 21, 2015*
How to get best benefit from treatment of Hypertension?

Lower?
Broader?
Earlier?
"Will lower blood pressure reduce the risk of heart and kidney diseases, stroke, or age-related declines in memory and thinking?"
SPRINT: Research Question

Examine effect of more intensive high blood pressure treatment than was recommended

Randomized Controlled Trial Target Systolic BP

Intensive Treatment
Goal SBP < 120 mm Hg

Standard Treatment
Goal SBP < 140 mm Hg
Cumulative Hazards for SPRINT Primary Outcome and All-Cause Mortality in Participants 75 and Older

No heterogeneity based on frailty status or gait speed

HR: 0.67 95% CI (0.51 to 0.86)
NNT = 28 at 3.26 years

HR: 0.68 95% CI (0.50 to 0.92)
NNT = 41 at 3.26 years

JAMA. 2016;315:2673-82
“If feasible, automated recording of multiple BP readings in the office with the patient seated in an isolated room … might be considered as a means to improve reproducibility and make office BP values closer to those provided by daytime ABPM or HBPM …”

European Heart Journal (2013) 34, 2159–2219
Let's Not SPRINT to Judgment About New Blood Pressure Goals

Eduardo Ortsil, MD, MPH, and Paul A. Jmes, MD

SPRINT (Systolic Blood Pressure Intervention Trial) investigators recently floated the idea of lowering blood pressure (BP) to less than 120 mm Hg with a target less than 140 mm Hg in patients at increased cardiovascular risk, a strategy that was stopped early as its results were promoted widely months before publication (1). Participants were mostly men (64%) with a mean age of 75 years and 5% had an increased cardiovascular risk, but patients with diabetes were excluded. With the lower treatment target, the trial found a 25% relative risk reduction in the primary composite outcome. Although a 25% reduction sounds impressive, it corresponded to a decrease in event rates from 6.8% to 5.2% over 2.2 years, or an absolute risk reduction of 0.6% (1). Thus, we estimate that for 1000 persons treated over 32 years to a systolic BP goal of less than 120 mm Hg compared with less than 140 mm Hg, an average of 16 persons will be benefitted, 22 persons will be seriously harmed, and 962 will not experience benefits or harms; however, one cannot predict who will be benefitted or be harmed. Patients may believe they are at risk for lower BP if they have received g 3 drugs every day for more than 3 years which might reduce their risk for cardiovascular events by 25%. However, after learning that their likelihood of absolute benefit is on ly 1.6%, with a greater likelihood of serious harms, their enthusiasm for more medications may diminish.

Based on SPRINT results, we estimate that for 1000 persons treated over 3.2 years to a systolic BP goal of less than 120 mm Hg, an average of 16 persons will benefit, 22 persons will be seriously harmed, and 962 will not experience benefits or harms; however, one cannot predict who will be benefitted or be harmed. Patients may be told that it is worthwhile to aim for lower BPs if they hear that receiving 3 drugs every day to lower the 3 years is might reduce their risk for cardiovascular events by 25%. However, after learning that their likelihood of absolute benefit is only 1.6%, with a greater likelihood of serious harm, their enthusiasm for more medications may diminish.
Optimal Blood Pressure Lowering in Coronary Artery Disease Patients: Blood Pressure In CAD

Is There A J Curve Phenomenon?
The Clarify Study

P. G. STEG. (Paris, FR), FP 5732
Study Design and Objectives

- Prospective longitudinal registry study of outpatients with stable CAD in 45 countries, treated for hypertension
- They used an arithmetic mean of all BP values measured throughout follow-up, with a Cox proportional hazards model, adjusted for all CV risk factors and treatments
- Primary outcome: composite of death, MI or stroke
- Secondary outcome: Each primary component, all cause death or hospitalised heart failure
Primary Outcome as a function of achieved BP

### Outcome by BP Group

<table>
<thead>
<tr>
<th>Outcome by BP Group</th>
<th>No. events / No. in group (%)</th>
<th>Hazard Ratio (95% CI); P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death, myocardial infarction, or stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP &lt; 120 mmHg</td>
<td>323 / 2687 (12.0)</td>
<td>1.56 [1.36 – 1.81]; &lt; 0.0001</td>
</tr>
<tr>
<td>SBP 120 - 129 mmHg</td>
<td>490 / 6938 (7.1)</td>
<td>1.00 (-)</td>
</tr>
<tr>
<td>SBP 130 - 139 mmHg</td>
<td>584 / 7578 (7.7)</td>
<td>1.08 (0.95 – 1.21); 0.2168</td>
</tr>
<tr>
<td>SBP 140 - 149 mmHg</td>
<td>386 / 3577 (10.8)</td>
<td>1.51 (1.32 – 1.73); &lt; 0.0001</td>
</tr>
<tr>
<td>SBP ≥ 150 mmHg</td>
<td>316 / 1859 (17.0)</td>
<td>2.48 (2.14 – 2.87); &lt; 0.0001</td>
</tr>
<tr>
<td>DBP &lt; 60 mmHg</td>
<td>50 / 214 (23.4)</td>
<td>2.01 (1.50 – 2.70); &lt; 0.0001</td>
</tr>
<tr>
<td>DBP 60 - 69 mmHg</td>
<td>351 / 2833 (12.4)</td>
<td>1.41 (1.24 – 1.61); &lt; 0.0001</td>
</tr>
<tr>
<td>DBP 70 - 79 mmHg</td>
<td>813 / 10802 (7.5)</td>
<td>1.00 (-)</td>
</tr>
<tr>
<td>DBP 80 - 89 mmHg</td>
<td>684 / 7667 (8.9)</td>
<td>1.41 (1.27 – 1.57); &lt; 0.0001</td>
</tr>
<tr>
<td>DBP ≥ 90 mmHg</td>
<td>201 / 1123 (17.9)</td>
<td>3.72 (3.15 – 4.38); &lt; 0.0001</td>
</tr>
</tbody>
</table>

Same results for all secondary components
Except stroke – no increased risk <120/70mmHg
But...Hypertension is more than just Blood Pressure!
Coexistence of Multiple CV Risk Factors

800 million people (1 in 8) have a BP $\geq 140/90$ mmHg

640M also have other uncontrolled CV risk factors
The Hypertensive Metabolic Phenotype

Hypertension

- Increased Triglycerides
- Hyperuricaemia
- Fatty Liver
- Insulin Resistance
- Increased Visceral Fat
- Decreased HDL-Cholesterol
- Small Dense LDL-Cholesterol
- Impaired Glucose Tolerance
Pathophysiology: Additive Effect of Cholesterol and BP on CHD Risk

ASCOT-LLA: non-fatal MI and fatal CHD

Combined Effect of LDL-C and SBP on Cardiovascular Events

N = 14,368 Major Vascular Events
What is the best approach to modern treatment of blood pressure to reduce risk?

- RAS blockade – ARB to reduce/regress structural damage, reduce inflammation and perhaps reduce risk of developing diabetes
  
  +

- CCB (Amlodipine) – complements ARB (potent BP reduction) and optimally reduces BP variability
  
  +

- Statin for most hypertensives – irrespective of baseline cholesterol to reduce cardiac and stroke risk
How Early Should We Treat Blood Pressure?
ALSPAC: Vascular Risk Factors at 9-11 yrs v. BMI

Blood pressure (mm Hg)

Systolic

Diastolic

Cholesterol (mmol/L)

Non-HDL Cholesterol

HDL Cholesterol

BMI (Kg/m²)
Childhood Obesity and Premature Death

- Glucose Intolerance
  1 v. 4th quartile
  73% higher deaths

- Childhood Hypertension
  1 v. 4th quartile
  57% higher deaths
Impact of High-Normal Blood Pressure on Risk of Major Cardiovascular Events* in Men

508 of 1337 subjects developed hypertension over 46 years
Midlife blood pressure predicts future diastolic dysfunction independently of blood pressure

Arjun Kumar Ghosh,¹,² Alun David Hughes,³ Darrel Francis,¹ Nishi Chaturvedi,³ Denis Pellerin,² John Deanfield,³ Diana Kuh,⁴ Jamil Mayet,¹ Rebecca Hardy,⁴ on behalf of the MRC NSHD Scientific and Data Collection Team

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**Graph: β coefficient for e' per 1 SD increase in systolic blood pressure**

- **36-43 years**
  - p < 0.001
- **43-53 years**
  - p = 0.2
- **53-60/64 years**
  - p < 0.001

Period of rate of change in systolic blood pressure

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Ghosh Heart 2016;102:1380–1387
Midlife Hypertension and 20-Year Cognitive Change
The Atherosclerosis Risk in Communities Neurocognitive Study

CONCLUSIONS AND RELEVANCE  Midlife hypertension and elevated midlife but not late-life systolic BP was associated with more cognitive decline during the 20 years of the study. Greater decline is found with higher midlife BP in whites than in African Americans.

BP (1990-92)  Gottesman JAMA Neurol 2014; 1646: E1-10
Effect of 1 mmol/L lower LDL-C & 10 mmHg lower SBP on Major Cardiovascular Events

SBP and LDL-C have independent, multiplicative and cumulative effects on CVD risk

B. Ference (Plymouth, US), FP 3163
Short-term (10-year) risk underestimates lifetime CV risk of young people with hypertension... Lifetime risk with untreated stage 1 hypertension in this age group could be substantial. Lifetime risk assessments may be a better way to inform treatment decisions and evaluate cost effectiveness of earlier drug therapy.
3g/day Reduction in Population Salt Intake

Cost saving after a decrease of even 1g/day achieved

Bibbins-Domingo NEJM 2010; 362: 590-599
Urinary Na Excretion and CV Events with and without Hypertension

Mente Lancet 2016; 388: 465–75

Falaschetti Lancet 2014; 383: 1912–19
Some Closing thoughts...

- BP remains major cause of premature death and disability
- Treatment reduces risk but ongoing challenges regarding detection, effective BP lowering and adherence
- Home monitoring and ABPM advantageous for diagnosis, pathophysiology and monitoring of treatment
Some More Closing thoughts…!

- Effective population strategy would prevent CVD and save many lives.
- But BP treatment is often too little and too late. Resistant hypertension is due to delayed treatment and vascular damage!
- Risk reduction requires going beyond BP control and combining other CV treatments such as statins—should be routine clinical practice!