Hypertension Contributes to the Development of Cardiovascular Disease

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

- **CAD**
  - Male: 22.7, Female: 9.5
  - Male: 45.4

- **Stroke**
  - Male: 3.3, Female: 2.4
  - Male: 12.4

- **PAD**
  - Male: 5.0, Female: 2.0
  - Male: 9.9

- **Cardiac failure**
  - Male: 3.5, Female: 2.1
  - Male: 13.9

**Risk ratio:**
- Male: 2.0, Female: 2.2
- Male: 3.8, Female: 2.6
- Male: 2.0, Female: 3.7
- Male: 4.0, Female: 3.0
Hypertension Remains Common

- World population is 6 Billion
- 1 in 6 have a Mobile phone
- 1 in 6 have Hypertension
Burden of hypertension in Asia

Hypertension affects approximately 1 billion people worldwide

2/3 in developing countries

1/3 adult in South-East Asia has hypertension

1.5 million people die of hypertension-related diseases each year in South-East Asia
Ischemic Heart Disease Mortality Rate in Each Decade of Age

Stable Angina (n=3949)
Myocardial Infarction (n=4486)
Ischaemic Stroke (n=937)
Cerebral Haemorrhage (n=434)

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

Rapsomaniki Lancet 2014; 383: 1899-1911
Complications of Hypertension: End-Organ Damage

Hypertension

Hemorrhage, Stroke

Retinopathy

Peripheral Vascular Disease

LVH, CHD, CHF

Renal Failure, Proteinuria

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 have we learnt about BP treatment?
NICE Guidelines 2011
Antihypertensive Drug Treatment

**Step 1**
- **Aged <55yrs**: A
- **Aged ≥55yrs**: C*

**Step 2**
- **Aged <55yrs**: A
- **Aged ≥55yrs**: C*

**Step 3**
- **Aged <55yrs**: A + C + D
- **Aged ≥55yrs**: A + C + D

**Step 4**
- **Resistant Hypertension**: A + C + D + Further Diuretic
  - Consider specialist Advice

**Drugs**:
- **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 spironolactone or higher dose thiazide
Combining antihypertensive agents is more efficacious than uptitration of monotherapy

![Bar chart showing incremental SBP reduction ratio of observed to expected additive effects for different classes of antihypertensive agents.]

- Thiazide: 1.04 (0.88–1.20)
- Beta blocker: 1.00 (0.76–1.24)
- ACE inhibitor: 1.16 (0.93–1.39)
- Calcium channel blocker: 0.89 (0.69–1.09)
- All Classes: 1.01 (0.90–1.12)

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

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)
Regardless of treatment, reducing blood pressure can reduce cardiovascular risk

Prespecified pooled cohort analysis from ACCOMPLISH (N=10,705)

ACCIMPLISH=Avoiding Cardiovascular events through COMbination therapy in Patients Livng with Systolic Hypertension; CV=cardiovascular; MI=myocardial infarction; SBP=systolic blood pressure
“Treating high blood pressure is cheaper than doing nothing”
What is new about BP detection and pathophysiology?
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
BP Is Variable: 24h Short-term

- Clinic BP
- Daytime BP
- Dipper
- HMBP
- Nighttime BP
- Morning BP

24h Average BP

BP Variability

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.
But...Hypertension is more than just Blood Pressure!
The Hypertensive Metabolic Phenotype

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

Deaths /10,000 Patient-years

N=316,099

Diabetes Increases Hypertension-Related CV Risk: MRFIT

Treating one risk factor does not eliminate risk of CV events

**Statin Trials**
- 4S
- AFCAPS/TexCAPS
- CARE
- LIPID
- WOSCOPS
- HPS
- PROSPER
- ALLHAT-LLT
- ASCOT-LLA

**Risk of primary event (%)**
- 70%
- 63%
- 76%
- 76%
- 69%
- 73%
- 85%
- 91%
- 64%

**Risk reduction (%)**
- 30%
- 37%
- 24%
- 24%
- 31%
- 27%
- 15%
- 9%
- 36%

**Events not avoided (%)**
- 70%
- 63%
- 76%
- 76%
- 69%
- 73%
- 85%
- 91%
- 64%

**BP Trials**
- SHEP (chlorthalidone +/- atenolol)
- MRC-O (HCTZ + atenolol)
- Syst-Eur (nitrendipine, enalapril, HCTZ)
- PROGRESS (perindopril +/- diuretic)

- 64%
- 75%
- 58%
- 72%

- 36%
- 25%
- 42%
- 28%
ASCOT-LLA: non-fatal MI and fatal CHD

**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
Angiotensin-Neprilysin Inhibition in Hypertension

Ruijope Lancet 2010; 375: 1255–66
Exposure to high BP is determinant of Target Organ Damage and this represents an opportunity for lifetime risk reduction.
BP Treatment in Type 2 DM

4733 age 62.2 years intensive vs standard BP treatment over 4.7 years

ACCORD Study Group NEJM 2010;362:1575-1585
Impact of High-Normal Blood Pressure on Risk of Major Cardiovascular Events* in Men

Blood Pressure:
- **High-Normal**: 130–139/85–89 mm Hg
- **Normal**: 120–129/80–84 mm Hg
- **Optimal**: <120/80 mm Hg

ALSPAC: Vascular Risk Factors at 9-11 yrs v. BMI

Blood pressure (mm Hg)
- Systolic
- Diastolic

Cholesterol (mmol/L)
- HDL Cholesterol
- Non-HDL Cholesterol

BMI (Kg/m²)
BMI and Hypertension: *Johns Hopkins Precursor Study*

508 of 1337 subjects developed hypertension over 46 years
Lifetime Risk of Hypertension for Age 30 years
>1m Subjects Without CVD During 5.2 years FU

Lifetime risk
for age 30 yrs
63.3 v 46.1%
Average 5 yrs lost

Rapsomaniki Lancet 2014; 383: 1899-1911
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.

Gottesman JAMA Neurol 2014; 1646: E1-10
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.
BP Management

How are we doing at population level?
3g/day Reduction in Population Salt Intake

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

Bibbins-Domingo NEJM 2010; 362: 590-599

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!