### Stroke Mortality

- The remarkable decline in stroke mortality has been acknowledged as one of the 10 great public health achievements for the United States (US) in the 20th century.
- Stroke has now fallen from the third to the fourth leading cause of death in the US.

### Mean Systolic Blood Pressure (SBP) by Time Period

<table>
<thead>
<tr>
<th>YEAR</th>
<th>SBP (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960-62</td>
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<tr>
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</tr>
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</tr>
<tr>
<td>2001-08</td>
<td>122 mm</td>
</tr>
</tbody>
</table>

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**Age-Adjusted Death Rates for Cerebrovascular Disease by Year—United States, 1900-2010**

Diseases were classified to the International Classification of Disease codes in use at the time the deaths were reported.

**Decline in Death Rates**

Per 100,000 population, standardized to the U.S. 2000 standard population

Diseases were classified to the International Classification of Disease codes in use at the time the deaths were reported.

**Population-Based Strategy**

SBP Distributions

**TABLE 1**

<table>
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</tr>
</tbody>
</table>
Summary for blood pressure shifts

- Declining shift in BP distribution consistent for different age groups
- Population-wide changes in reduced blood pressures associated with large accelerated reductions in stroke mortality
- Shift in mean arterial blood pressure is more pronounced in older Americans than younger Americans

Risk of Stroke begins at BP below 140/90 mmHg

- Meta-analysis of 61 prospective studies observed 1M adults between the ages of 40-69 years with starting BP of 115/75 mmHg
- Each incremental 20 mmHg (SBP) and 10 mmHg (DBP) was associated with a 2x increase in stroke death rates
- This effect is seen in all decades of life.
Observational Studies

- Higher the BP = Increase in stroke mortality rate
- 34.6% for HTN: INTERSTROKE study concluded the contribution of various stroke factors to the burden of stroke worldwide
- 45% of all strokes attributed to uncontrolled BP
- HBP identified as responsible for largest number of cardiovascular and stroke deaths in US


Clinical Trials: Benefit of HTN Treatment to Reduce Stroke Risks

- Antihypertensive therapy has been associated with reductions:
  - Stroke incidence averaging 35-40%
  - Myocardial infarction 20-25%
  - Heart failure more than 50%

Reducing SBP even if BP control levels are not achieved improves risks and outcomes.


Clinical Trials: Reduction of Recurrent Strokes

- Secondary Prevention
  - Dutch TIA Trial Study and others have shown significantly lower rates of recurrent stroke with lower blood pressures
  - Secondary Prevention of Small Subcortical Strokes (SPS3) Trial

showed targeting a systolic blood pressure
< 130 mmHg is likely to reduce recurrent stroke by about 20% and significantly reduced intracerebral hemorrhage by 2/3


Systolic Blood Pressure by Treatment Groups

Efficacy Outcomes (lancet. 2013 Aug 10;382(991):507-15)

<table>
<thead>
<tr>
<th></th>
<th>Higher Target</th>
<th>Lower Target</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke</td>
<td>152 2.8</td>
<td>125 2.3</td>
<td>0.81 (0.64, 1.03)</td>
<td>0.08</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>131 2.4</td>
<td>112 2.0</td>
<td>0.84 (0.66, 1.09)</td>
<td>0.19</td>
</tr>
<tr>
<td>Intracerebral</td>
<td>16 0.29</td>
<td>6 0.11</td>
<td>0.37 (0.15, 0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>188 3.4</td>
<td>158 3.0</td>
<td>0.84 (0.66, 1.04)</td>
<td>0.10</td>
</tr>
<tr>
<td>Major vascular event</td>
<td>188 3.4</td>
<td>158 3.0</td>
<td>0.84 (0.66, 1.04)</td>
<td>0.10</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>40 0.70</td>
<td>35 0.62</td>
<td>0.88 (0.55, 1.39)</td>
<td>0.59</td>
</tr>
<tr>
<td>Deaths</td>
<td>181 1.74  106 1.6</td>
<td>1.63 (0.79, 1.39)</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Vascular death</td>
<td>181 1.74  106 1.6</td>
<td>1.63 (0.79, 1.39)</td>
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</tr>
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Evolution of SBP Classification
Treatment Guidelines

- JNC’s BP treatment guidelines have included recommendations focused on lowering HTN-related conditions including stroke.
- With each set of JNC guidelines, the BP level for treatment and goals has typically been lowered, possibly impacting the population BP levels as SBPs have been lower (Table 1).

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*Stroke. 45(1):315-53, 2014*

Structured Programs to Lower Stroke Risks

- Structured programs are used to implement public health programs that focus on decreasing blood pressure and therefore stroke risks.
- Programs are aimed at working with manufacturers, restaurants, and food procurement policymakers to decrease stroke risk factors via:
  - Reduction of salt in prepared and processed food
  - Encouragement of fresh produce consumption
  - Increasing community participation in physical activity
  - Detecting and tracking HBP at community places

*Stroke. 45(1):315-53, 2014*

**TABLE 1**

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*Stroke. 45(1):315-53, 2014*

HTN – Summary

“Higher BP = Greater Stroke Risk”

- Observational epidemiological study findings are consistent with clinical trial findings that BP reduction results in lower stroke mortality rates
- Major determinant for decrease in stroke prevalence and mortality → decrease in BP with drug therapy

*Stroke. 45(1):315-53, 2014*

Comparison of Hypertension Guidelines 2011-2014

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition of Hypertension</td>
<td>≥ 140/90</td>
<td>≥ 140/90</td>
<td>≥ 140/90</td>
<td>≥ 140/90</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Drug therapy in low risk patients</td>
<td>≥ 140/90</td>
<td>≥ 140/90</td>
<td>≥ 140/90</td>
<td>≥ 140/90</td>
<td>≥ 140/90</td>
</tr>
<tr>
<td>Blood pressure targets</td>
<td>&lt; 140 y.</td>
<td>&lt; 140 y.</td>
<td>&lt; 140 y.</td>
<td>&lt; 140 y.</td>
<td>&lt; 140 y.</td>
</tr>
<tr>
<td>Elderly &lt; 80 y.</td>
<td>SBP 140-150</td>
<td>SBP ≤ 140</td>
<td>SBP ≤ 140</td>
<td>SBP ≤ 140</td>
<td>SBP ≤ 140</td>
</tr>
<tr>
<td>Elderly ≥ 80 y.</td>
<td>SBP 140-150</td>
<td>SBP ≤ 140</td>
<td>SBP ≤ 140</td>
<td>SBP ≤ 140</td>
<td>SBP ≤ 140</td>
</tr>
</tbody>
</table>


Recommendation 1

- In the general population ≥60 years of age, initiate pharmacologic treatment to lower BP at SBP ≥150 mm Hg or DBP ≥90 mm Hg and treat to a goal SBP <150 mm Hg and goal DBP <90 mm Hg.
  - Strong Recommendation – Grade A

- Corollary Recommendation: In the general population ≥60 years of age, if pharmacological treatment for high BP results in lower achieved SBPs (for example, <140 mm Hg) and treatment is not associated with adverse effects on health or quality of life, treatment does not need to be adjusted.
  - Expert Opinion – Grade E

*JAMA. 2014;311(5):507-520*
2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Table 6: Guideline Comparisons of Goal BP and Initial Drug Therapy for Adults With Hypertension

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Population</th>
<th>Goal BP, mm Hg</th>
<th>Initial Drug Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014 Hypertension guideline</td>
<td>General &lt;60 y</td>
<td>≤130/80</td>
<td>Intensive: thiazide type diuretics, ACEI, ARB, or CCB; general: thiazide type diuretics or CCB</td>
</tr>
<tr>
<td></td>
<td>General &lt;60 y</td>
<td>≤130/80</td>
<td>Thiazide type diuretics, ARB, or CCB</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>≤130/80</td>
<td>Thiazide type diuretics, ARB, or CCB</td>
</tr>
<tr>
<td></td>
<td>CKD</td>
<td>≤140/90</td>
<td>ACEI or ARB</td>
</tr>
</tbody>
</table>

Where ASH and the JAMA JNC paper agreed.

- “The treatment goal for systolic blood pressure is usually ≤140 mm Hg and for diastolic blood pressure <90 mm Hg. In the past, guidelines have recommended treatment values of <130/80 mm Hg for patients with diabetes, chronic kidney disease, and coronary artery disease. However, evidence to support this lower target in patients with these conditions is lacking…”

Where do ASH and the JAMA JNC 8 diverge on SBP Thresholds and goals?

- For patients older than 80 years, the suggested threshold for starting treatment is at levels ≥150/90 mm Hg. Thus, the target of treatment should be ≤140/90 mm Hg for most patients but ≤150/90 mm Hg for older patients (unless these patients have chronic kidney disease or diabetes, when ≤140/90 mm Hg can be considered).

Treatment Goals and Thresholds in Older individuals

- Biggest area of diversion is between 60 and 79 years old
- There is more general agreement for those for individuals 80 and over, particularly if they are fragile, that the treatment goal should be seriously considered 150/90 rather than 140/90

Treatment Goals and Thresholds in Older individuals

- This includes the expert opinion that if an individual is doing well on treatment there is no compelling reason to reduce the intensity of treatment at a specific age.
- Fragile not defined – consider fall risk, multiple medications, and CKD
- Other guidelines Canadian, UK and ESH/ESC all support the 150/90 goal for those 80 and older.
RECOMMENDATIONS

1. The \(<140/90\)-mm Hg BP target is reasonable for the secondary prevention of cardiovascular events in patients with hypertension and CAD (Class IIa; Level of Evidence: B).

2. A lower target BP (<130/80 mm Hg) may be appropriate in some individuals with CAD, previous MI, stroke or transient ischemic attack, or CAD risk equivalents (carotid artery disease, PAD, abdominal aortic aneurysm) (Class IIb; Level of Evidence: B).

Hypertension Recommendations from 2014 Stroke Prevention Guidelines

Initiation of BP therapy is indicated for previously untreated patients with ischemic stroke or TIA who, after the first several days, have an established BP \(\geq 140\) mm Hg systolic or \(\geq 90\) mm Hg diastolic (Class I; Level of Evidence B). Initiation of therapy for patients with BP \(<140\) mm Hg systolic and \(<90\) mm Hg diastolic is of uncertain benefit (Class IIb; Level of Evidence C). (Revised recommendation)
COMPARISON OF PERSPECTIVE

Majority Perspective
- HYVET, Syst-Eur and SHEP showed benefit but had average SBP in the active arm was between 143 and 150 mm Hg.
- Only two other studies had average SBP in the active arm was 143 and 150 mm Hg.
- Evidence from trials and observational studies that the panel did not use as part of its review supports the lower goal, especially in high-risk patients.
- Two large meta-analysis supported the < 140 goal.
- Inconsistency on lower goal ok for Diabetes but not other high risk groups.

Minority Perspective
- Evidence from trials and observational studies that the panel did not use as part of its review supports the lower goal, especially in high-risk patients.
- Two large meta-analysis supported the < 140 goal.
- Inconsistency on lower goal ok for Diabetes but not other high risk groups.

These differing perspectives were reflected within the Appointed JNC 8 Panel

Majority Perspective
- Simplify the goals (of treatment because) there are only two goals to remember.
- Physicians who take care of the elderly have been concerned over the years about the potential for causing harm by over-treating blood pressure.
- “It’s certainly not uncommon for elderly patients to become dizzy on standing because of the antihypertensive medications they take. Such patients are at an increased risk for falls and their sequelae”. (Paul James)

Minority Perspective
- What is the trial evidence of increase risk of serious adverse events with treatment to < 140 mm Hg?
- JATOS, VALISH, and SPS3 all concluded that lower goal was safe.

US CVD Death Rates for Individuals < and > than 65 years

Condition (Cause of death by underlying Cause)

<table>
<thead>
<tr>
<th>Age &lt; 65 or ≥ 65 years</th>
<th>1999-2010</th>
<th>1989-1998</th>
<th>1999-2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 65 or ≥ 65 years</td>
<td>30</td>
<td>-3.6</td>
<td>-3.4</td>
</tr>
<tr>
<td>Coronary Disease</td>
<td></td>
<td>-2.7</td>
<td>-5.6</td>
</tr>
<tr>
<td>Coronary Disease</td>
<td></td>
<td>-1.3</td>
<td>-2.3</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>-0.9</td>
<td>-5.3</td>
</tr>
</tbody>
</table>

Systolic Blood Pressure by Treatment Groups

- At 1 yr follow-up average SBPs were 138 vs. 127 mm Hg
- Last observed visit, average SBP difference between groups was 11 mm Hg

Serious Adverse related to hypotension: SPS3
SPS 3 Side effects potentially related to BP management

Concerns about the move to a higher BP goal
- Increasing the systolic BP target in those 60 years or older will have the effect of reducing the intensity of antihypertensive treatment among patients already being treated, among them a large population with established CVD or at high risk for CVD (including African Americans and patients with multiple CVD risk factors other than chronic kidney disease).
- Raising the target may have the unintended effect of reversing decades of declining CVD rates, especially stroke mortality.

Diabetes Treatment and Effect on Stroke Prevalence
- Diabetes mellitus is a risk factor for stroke and stroke mortality
- Diabetes prevalence has been increasing in US and the world
- Sparse data are available regarding trends in population prevalence of diabetes treatment or treatment intensity
- Temporal effect of changes in diabetes treatment on risk of stroke death cannot be determined


Contribution of Diabetes Treatment and Control on Decline in Stroke

Diabetes Treatment and Effect on Stroke Prevalence
- The rise in comorbid diabetes over time was more pronounced in patients who were relatively younger, Black, other minority groups, or Medicaid beneficiaries
- Factors independently associated with higher odds of diabetes in acute ischemic stroke patients were Black/other vs. White race, congestive heart failure, peripheral vascular disease, history of myocardial infarction, renal disease, and HTN.


Diabetes Treatment and Effect on Stroke Prevalence
- Ischemic stroke incidences have decreased in US
- Acute ischemic stroke (AIS) hospitalizations in us from 1997-2006 showed a decline by 17%


Diabetes Treatment and Effect on Stroke Prevalence
- Ischemic stroke and co-morbid diabetes incidences have increased in US
- AIS hospitalizations with co-morbid type 2 diabetes rose by 27% from 1997-2006


Diabetes Treatment and Effect on Stroke Prevalence
- The rise in comorbid diabetes over time was more pronounced in patients who were relatively younger, Black, other minority groups, or Medicaid beneficiaries
- Factors independently associated with higher odds of diabetes in acute ischemic stroke patients were Black/other vs. White race, congestive heart failure, peripheral vascular disease, history of myocardial infarction, renal disease, and HTN.

**Diabetes Treatment and Effect on Stroke Prevalence**

- Main thrust of diabetes research treatment –
  Investigate whether tight glucose treatment would improve long-term outcomes
- Meta-analysis showed that tight glucose control did affect MI and CAD events, but had no consistent effect on stroke events.
- There was a suggestion that tight glucose control may increase mortality according to ACCORD trial results.

**Diabetes Treatment and ACCORD study**

- ACCORD sub-study found that patients with type 2 diabetes had reduced risk for stroke if blood pressure was tightly controlled.
- ACCORD and other studies suggest that multi-factorial risk factor intervention and tight blood pressure control lowers risk for stroke in patients with diabetes.

**Summary : Diabetes Treatment and Effect on Stroke Prevalence**

- Tight glucose control for type 2 diabetic patients has not been shown to reduce mortality from stroke (based on a meta-analysis) and in fact led to a higher mortality in one large RCT.
- Multi-factorial risk factor intervention in diabetic patients, especially blood pressure control, has been shown to reduce mortality and stroke.

**Summary**

- After 50 years, goal SBP recommendations have consistently be lowered to the current 140/90 in conjunction with lowering in the distribution of population blood pressures and lowered associated outcomes including stroke.
- Randomized control trial evidence is unclear for 140/90 while observational studies are strong.

**Conclusions**

- Is the glass half full or half empty?
- Is the rate of hypertension control – half under control or half uncontrolled?
- Do we raise target blood pressure to 150 until the evidence supports 140, OR do we stay at 140 until the trials support no value?