Treatment of arterial hypertension in older people - can we rely enough on evidence?

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Department of Geriatrics
Ghent University Hospital

Symposium Belgian Hypertension Committee
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Hypertension after 80 y: Active tt (indapamide ± perindopril) vs. placebo: The HYVET study

All Stroke

Stroke Death

All cause mortality

NCV/Unknown death

CV Death

Cardiac Death

Heart Failure

CV events

NEJM 2008; 358:1887-1898
SPRINT: A Randomized Trial of Intensive versus Standard Blood-Pressure Control

- Randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to
  - a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or
  - a target of less than 140 mm Hg (standard treatment)
- The primary composite outcome: myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

NEJM 2015;373:2103-16
At 1 year, the mean systolic blood pressure was
- 121.4 mm Hg in the intensive treatment group and
- 136.2 mm Hg in the standard-treatment group.

The intervention was stopped early after a median follow-up of 3.26 years owing to
- a significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment group (1.65% per year vs. 2.19% per year; hazard ratio with intensive treatment, 0.75; 95% confidence interval [CI], 0.64 to 0.89; P<0.001).

All-cause mortality was also significantly lower in the intensive treatment group (hazard ratio, 0.73; 95% CI, 0.60 to 0.90; P = 0.003).

Rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the intensive treatment group than in the standard-treatment group.
**SPRINT:** A Randomized Trial of Intensive versus Standard Blood-Pressure Control

- **CONCLUSIONS**
- Among patients at high risk for cardiovascular events but without diabetes, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in
  - lower rates of fatal and nonfatal major cardiovascular events and death from any cause
  - although significantly higher rates of some adverse events were observed in the intensive-treatment group.
The results of SPRINT add substantially to the evidence of benefits of lowering systolic blood pressure, especially in older patients with hypertension.

Whereas there are no eligibility criteria specific to the senior subgroup other than age, the general eligibility criteria were influenced by consideration of factors of importance to the inclusion of older participants in SPRINT, including cognitive status, orthostasis, transportation, and site of residence (e.g., nursing home).

The goal is to assemble a representative population of older patients for whom intensive BP lowering is reasonable to consider from a medical perspective. This goal is motivated by the perspective that there may be some older persons with advanced frailty and/or multiple comorbid conditions whose health is so poor that it would not be reasonable to attempt to treat SBP as intensively as needed to control SBP to less than 120 mm Hg.
Role of blood pressure and arterial stiffness on morbidity, mortality and cognitive impairment in very old people living in nursing homes

- 1126 subjects
- 78% women
- Age: 87y at baseline
- 7.2 drugs/day
- 2-year follow up
HYVET vs. PARTAGE: Major differences in patients’ CV profile

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Active Treatment (N = 1933)</th>
<th>Placebo (N = 1912)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>83.6±3.2</td>
<td>83.5±3.1</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>1174 (60.7)</td>
<td>1152 (60.3)</td>
</tr>
<tr>
<td>Blood pressure — mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>While sitting</td>
<td>173.0±8.4/90.8±8.5</td>
<td>173.0±8.4/90.8±8.5</td>
</tr>
<tr>
<td>While standing</td>
<td>168.0±11.0/88.7±9.3</td>
<td>167.9±11.1/88.6±9.3</td>
</tr>
<tr>
<td>Orthostatic hypotension — no. (%)</td>
<td>152 (7.9)</td>
<td>169 (8.8)</td>
</tr>
<tr>
<td>Isolated systolic hypertension — no. (%)</td>
<td>625 (32.3)</td>
<td>623 (32.6)</td>
</tr>
<tr>
<td>Heart rate — beats/min</td>
<td>74.5±9.1</td>
<td>74.5±9.3</td>
</tr>
</tbody>
</table>

**Cardiovascular history**

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<th>Characteristic</th>
<th>Active Treatment (N = 1933)</th>
<th>Placebo (N = 1912)</th>
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</thead>
<tbody>
<tr>
<td>Cardiovascular disease — no. (%)</td>
<td>223 (11.5)</td>
<td>229 (12.0)</td>
</tr>
<tr>
<td>Hypertension — no. (%)</td>
<td>1737 (89.9)</td>
<td>1718 (89.9)</td>
</tr>
<tr>
<td>Antihypertensive treatment — no. (%)</td>
<td>1241 (64.2)</td>
<td>1245 (64.1)</td>
</tr>
<tr>
<td>Stroke — no. (%)</td>
<td>130 (6.7)</td>
<td>131 (6.9)</td>
</tr>
<tr>
<td>Myocardial infarction — no. (%)</td>
<td>59 (3.1)</td>
<td>52 (3.2)</td>
</tr>
<tr>
<td>Heart failure — no. (%)</td>
<td>56 (2.9)</td>
<td>55 (2.9)</td>
</tr>
</tbody>
</table>

**CV disease (%)**

- HYVET: 17%
- PARTAGE: 52%

*J Hypertens 2010  JACC 2012*
Flow chart with the data concerning deaths and major CV events in the PARTAGE population during the 2-year follow up period.

Total population enrolled
1126 (100%)

Major CV events: 228 (20.2%)

Initial lethal CV event: 85 (7.5%)

Initial non-lethal CV event: 143 (12.7%)

Subsequent lethal CV event: 32 (2.8%)

(f) Alive at the end: 96 (8.5%)

(d) Lost to follow up: 5 (0.4%)

Subsequent non-CV death: 10 (0.9%)

(e) Alive at the end without Major CV events: 743 (66.0%)

(a) Total CV deaths: 117 (10.4%)

(c) Lost to follow up: 35 (3.1%)

Non-CV Mortality: 120 (10.7%)

(b) Total non-CV deaths: 130 (11.5%)

(c)+(d) lost to follow up: 40

(e)+(f) alive at the end of the follow up: 839

Total: 1126

(d) Lost to follow up: 5 (0.4%)
What is the profile of the subjects with low BP having increased total mortality?
Antihypertensive medication in the PARTAGE study

TOTAL POPULATION N= 1126

TREATED for HYPERTENSION N=814

TREATED with >1 drug for HYPERTENSION N=650
Mean Nb of antiHTn drugs: 2.7/d

Conclusion: 58% of the residents over 80 receive combination antihypertensive therapy

J Hypertens 2012
JAMA Int Med 2015
Original Investigation

Treatment With Multiple Blood Pressure Medications, Achieved Blood Pressure, and Mortality in Older Nursing Home Residents

The PARTAGE Study

Athanase Benetos, MD, PhD; Carlos Labat, BSc; Patrick Rossignol, MD, PhD; Renaud Fay, PharmD; Yves Rolland, MD, PhD; Filippo Valbusa, MD; Paolo Salvi, MD, PhD; Mauro Zamboni, MD, PhD; Patrick Manckoundia, MD, PhD; Olivier Hanon, MD, PhD; Sylvie Gautier, MD

Published online February 16, 2015.
Over-mortality (2x) in patients with low SBP (<130 mmHg) under combination of anti-hypertensive therapy

20% of the entire population

Hazard ratios for all-cause mortality according to SBP levels, number of antihypertensive drugs and their interaction, both unadjusted (panel A) and after adjustment for several co-founders.

### Unadjusted Analysis

<table>
<thead>
<tr>
<th>Condition</th>
<th>HR (95% CI)</th>
<th>Better Prognosis</th>
<th>Worse Prognosis</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP &lt;130 mm Hg</td>
<td>0.83 (0.53-1.31)</td>
<td></td>
<td></td>
<td>.42</td>
</tr>
<tr>
<td>≥2 Anti-HTN drugs</td>
<td>0.97 (0.70-1.33)</td>
<td></td>
<td></td>
<td>.83</td>
</tr>
<tr>
<td>SBP &lt;130 mm Hg and ≥2 anti-HTN drugs</td>
<td>2.13 (1.23-3.69)</td>
<td></td>
<td></td>
<td>.007</td>
</tr>
</tbody>
</table>

### Adjusted Analysis

<table>
<thead>
<tr>
<th>Condition</th>
<th>HR (95% CI)</th>
<th>Better Prognosis</th>
<th>Worse Prognosis</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP &lt;130 mm Hg</td>
<td>0.75 (0.46-1.22)</td>
<td></td>
<td></td>
<td>.25</td>
</tr>
<tr>
<td>≥2 Anti-HTN drugs</td>
<td>1.16 (0.82-1.64)</td>
<td></td>
<td></td>
<td>.41</td>
</tr>
<tr>
<td>SBP &lt;130 mm Hg and ≥2 anti-HTN drugs</td>
<td>2.09 (1.16-3.77)</td>
<td></td>
<td></td>
<td>.01</td>
</tr>
<tr>
<td>Age, per 5 y</td>
<td>1.25 (1.10-1.42)</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.63 (1.22-2.17)</td>
<td></td>
<td></td>
<td>.01</td>
</tr>
<tr>
<td>BMI ≤25</td>
<td>1.57 (1.19-2.06)</td>
<td></td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>Charlson Comorbidity Index score, per 1-point increase</td>
<td>1.09 (1.03-1.16)</td>
<td></td>
<td></td>
<td>.005</td>
</tr>
<tr>
<td>ADL score, per 1-point increase</td>
<td>0.77 (0.68-0.86)</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Benetos A et al, JAMA Int. Med 2015
172 patients (79±5 years, 63% female), 68% with dementia and 32% MCI

BP measurement, drug treatment, ABPM, Clinical, Cognitive and Functional evaluation at baseline and follow-up (12 Months)

Mossello E et al, JAMA Int Med, 2015
Mossello E et al, JAMA Int Med, 2015
Drug-induced low BP may be responsible for decreased perfusion of key organs (heart, brain, kidney…) in very old frail subjects.

Should we modify our therapeutic strategy in these patients?
The association of SBP (>160 mmHg) with all-cause mortality differs in older adults with slow, medium, and fast walking speed.

Cox proportional hazards model, adjusted for age, gender, cognitive function, creatinine, interleukin-6, and diabetes medication use.
No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the HYpertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over

Jane Warwick¹, Emanuela Falaschetti², Kenneth Rockwood³, Arnold Mitnitski⁴, Lutgarde Thijs⁵, Nigel Beckett⁶, Christopher Bulpitt⁶ and Ruth Peters²
The applicability of the results to the wider older population has been questioned, so that uncertainty remains as to whether treatment benefits also extend to the frailer elderly people.

To investigate further, we calculated the Frailty Index (FI) for all available HYVET study participants and obtained frailty-adjusted estimates of the effect of antihypertensive treatment in very elderly people.

Warwick J et al, BMC 2015
Distribution and FI in the HYVET population

Figure 1: Histogram showing the distribution of frailty index (FI) among 2,656 participants of HYVET at entry to the study.

Warwick J et al, BMC 2015
In the HYVET study participants there was no evidence of an interaction between treatment effect and frailty.

Both the frailer and the fitter older adults with hypertension appeared to gain from treatment.

Warwick J et al, BMC 2015
HYVET vs. PARTAGE

Which % of PARTAGE hypertensive patients had the criteria to be included in the HYVET study?

- 75%
- 50%
- 25%
- 10%
- 0%
What do the guidelines propose in the presence of low BP under anti-Htn treatment?
### 2013 ESH/ESC Guidelines for the management of arterial hypertension (Mancia et al J. Hypert 2013)

#### Antihypertensive treatment strategies in the elderly

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Ref.&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg.</td>
<td>I</td>
<td>A</td>
<td>141, 265</td>
</tr>
<tr>
<td>In fit elderly patients &lt;80 years old antihypertensive treatment may be considered at SBP values ≥140 mmHg with a target SBP &lt;140 mmHg if treatment is well tolerated.</td>
<td>IIb</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>In individuals older than 80 years with an initial SBP ≥160 mmHg it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions.</td>
<td>I</td>
<td>B</td>
<td>287</td>
</tr>
</tbody>
</table>
2013 ESH/ESC Guidelines for the management of arterial hypertension
Anti-hypertensive treatment strategies in old people

| In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment. |
| Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes octogenarian. |

Mancia G et al, J. Hypertens 2013
Care of the Aging Patient: From Evidence to Action

Polypharmacy in the Aging Patient Management of Hypertension in Octogenarians

Athanase Benetos, MD, PhD; Patrick Rossignol, MD, PhD; Antonio Cherubini, MD, PhD; Laure Joly, MD, PhD; Tomasz Grodzicki, MD, PhD; Chakravarthi Rajkumar, MD, PhD; Timo E. Strandberg, MD, PhD; Mirko Petrovic, MD, PhD
Figure. Decisional Algorithm for the Management of Hypertensive Patients Older Than 80 Years

Individual aged ≥80 y with systolic BP >160 mm Hg

Robust

Perform rapid assessment for frailty (see Box)

Frail

Perform Comprehensive Geriatric Assessment, including evaluation of Functional capacities Cognitive status Polypharmacy Prioritize therapeutic goals

Target systolic BP 130–150 mm Hg

Therapeutic approach similar to individuals aged 65–75 y Start with monotherapy Avoid use of >3 antihypertensive drugs Always check for orthostatic hypotension Optimize treatment for global cardiovascular disease protection

Target systolic BP 150 mm Hg

Begin antihypertensive treatment with monotherapy at a low dose Increase dose slowly

If SBP <130 mm Hg or orthostatic hypotension occurs Consider reducing antihypertensive treatment, especially if combination therapy Identify and correct other factors, including medications that may be decreasing BP

Benetos A et al; JAMA. 2015;314:170-180
ROBUST (FIT) SUBJECTS

- Focus on SBP and PP, target SBP 130-150 mmHg
- Start with monotherapy; avoid using more than 3 antihypertensive drugs
- Always check for orthostatic hypotension
- Optimize treatment for global CVD protection
THM (2): TREATING HYPERTENSIVE INDIVIDUALS OVER 80 YEARS OLD

FRAIL SUBJECTS

- Reconciliation and revision of the prescription
- Evaluation (CGA) of the risk/benefit ratio (life expectancy, geriatric syndromes, polypharmacy, etc.)
- Start anti-HTn treatment with one drug; start low and go slowly, SBP goal 150 mmHg
- Identify/correct other factors/drugs decreasing BP
- If SBP<130 mmHg or orthostatic hypotension under treatment: Consider reducing antihypertensive treatment, especially in case of combination therapy
Conclusions

There is limited evidence to support recommendations for hypertension treatment of frail, very old patients. When treating hypertension in older patients, international guidelines and each patient’s overall clinical condition should be considered. The guidelines suggest reducing SBP to between 140 and 150 mm Hg and avoiding having SBP lower than 130 mm Hg. This can be achieved by appropriate hydration and nutrition, reduction or cessation of other drugs that can decrease blood pressure and, if necessary, progressive reduction of antihypertensive treatment. All medications should be regularly reviewed to determine if they are necessary.
Concrete actions to improve clinical practice

Working group ESH/EUGMS to revisit the guidelines for frail very old subjects

Impact of the REduction in antihypertensive TREATment on total mortality in FRAIL older subjects with low SBP - Randomized, controlled study in subjects over 80 years living in nursing homes: The RETREAT FRAIL study