

# Treating hypertension in people over 80 years old: One size does not fit all

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## ABSTRACT

Hypertension is highly prevalent among adults over 80 years old. Clinical evidence supports the beneficial effects of lowering blood pressure in community-dwelling, hypertensive individuals over 80 years of age presenting a vigorous health. However, observational studies in frail older individuals have shown no or even an inverse relationship between both systolic and diastolic blood pressure and morbidity-mortality. These contrasting results in old hypertensive individuals reflect the considerable functional heterogeneity of the elderly; they suggest that functional status rather than chronological age should guide therapeutic strategies. Thus, the guidelines of hypertension treatment in robust older individuals cannot be extrapolated to very old, frail individuals, who have been excluded from the above clinical trials.

Accordingly, we propose that:

- Functional status and frailty should be assessed in all 80+ people, and taken into account in the decision of antihypertensive treatment strategies
- Observational studies and registries should be amplified in this population
- Controlled trials are necessary in the most frail subjects in order to obtain strong evidence for the benefits of the different therapeutic strategies.

Clearly, in the very old subjects, the therapeutic strategy "one size fits all" cannot be applied due to the enormous functional heterogeneity in these people. Precision medicine approaches should be developed taking into account both the cardiovascular risk profile and the function/autonomy status of these subjects.

## People over 80 years old: Functional profiles and blood pressure regulation

Over the last 40 years, the population over 80 years of age has expanded substantially. This part of the population is the most rapidly increasing age group in the western societies. Currently, life expectancy for these individuals living in the Organisation for Economic Co-operation and Development (OECD) group of countries is approximately 9 years compared to about 6 years in the 1970's, corresponding to an increase of 50%<sup>1</sup>. The continuously increasing number of people over 80 years of age has led to a growing population prone to multimorbidity, frailty<sup>2</sup>, polypharmacy and partial or

complete loss of autonomy. Thus, the number of very old frail people with pronounced frailty and limited autonomy has increased during the last decade all over the world<sup>3</sup>; many of these subjects live in Nursing Homes (NH). In 2013, in the European Union there were 3.7 million long-term care beds in nursing and residential care facilities. This number increased in most European countries between 2011 and 2014. For example, during this period, NH beds increased in France from about 611,000 to 634,500 and in Italy from 220,000 to 234,000. In addition to the individuals living in NHs, many community-dwelling older persons have advanced frailty with limited autonomy; they too re-

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quire assistance for basic daily activities. Data from the French National Institute of Statistics and Economic Studies<sup>4</sup> show that among individuals over 75 years old, 750,000 live in the community and receive Autonomy Personalised Allocation (APA) in addition to 550,000 APA recipients who live in NHs.

In terms of cardiovascular disease, subjects over 80 years present 2 characteristics:

- a) Cardiovascular deaths are by far the most common cause of mortality<sup>5</sup> whereas before the age of 80 years old cancers are the most common cause of death.
- b) The prevalence of high BP is estimated more than 70%<sup>6</sup> and the vast majority of these patients received antihypertensive medication

High BP, in particular high systolic BP, is a clinical expression of arterial stiffness<sup>7</sup> that develops during the aging process. In the past, the increase in systolic and pulse pressure (PP) was considered part of the normal aging process and thus was deemed not to require therapeutic intervention. We now know that older subjects with higher levels of SBP and PP not only have higher cardiovascular morbidity and mortality<sup>8</sup> but also exhibit a higher prevalence of other age-related diseases<sup>9,10</sup>, loss of autonomy and shorter life expectancy<sup>11</sup>. However, the association between SBP and morbidity and mortality is not observed in old very frail individuals, with several co-morbidities and significant functional decline. In these individuals, low SBP levels may not be a sign of so-called “good arterial health” but often a sign of comorbidities such as malnutrition, heart failure, neurological disorders, etc. as well as other concomitant conditions associated with poor prognosis. In addition people with marked frailty and polymorbidity could present altered circulatory autoregulation, causing tissue hypo-perfusion in presence of low BP especially when these low BP values are due to multiple antihypertensive drugs. Thus a low BP (example SBP<130 mmHg) in these individuals in response to therapy might increase rather than decrease morbidity and mortality. Therefore, information provided by BP measurements in predicting cardiovascular risk may be misleading. Currently, the majority of evidence regarding the risks of high BP as well as the benefits from its correction is derived from a simple extrapolation of data obtained in younger populations and in selected robust older individuals.

### The clinical evidence for treating high BP in people 80+

The Hypertension in the Very Elderly Treatment (HYVET) study<sup>12</sup> is the only controlled randomized trial designed to answer the question whether antihypertensive treatment can reduce morbidity and mortality in patients older than 80 years. Patients enrolled in that study had an SBP at inclusion of >160 mmHg independently of diastolic BP (DBP) levels, and the goal SBP was an SBP<150 mmHg. The results of the HYVET study, published in 2008, showed beneficial effects of the active treatment (diuretic associated with angiotensin converting enzyme inhibitors (ACEI) if necessary) as compared to the placebo for most of the predefined endpoints. For the remaining endpoints including the principal endpoint (all strokes) the same trend was observed but the level of significance had not been reached probably because of the premature interruption of the study due to a much lower total mortality in the intervention group. Based on these considerations, the 2013 ESC-ESH Guidelines<sup>8</sup> for the management of arterial hypertension stated that “in the elderly” over 80 years old, evidence is limited to individuals with initial SBP of >160 mmHg, whose SBP was reduced to values <150. Therefore, this recommendation is evidence-based.

Post hoc analysis of the HYVET trial did not find a relationship between the benefit of anti-hypertensive treatment and patients’ frailty<sup>13</sup> This is reassuring for community-dwelling older hypertensives, but an important limitation of the HYVET study is the exclusion of all subjects with major frailty<sup>12</sup> (Table 1). This led the European guidelines to conclude that 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”<sup>8</sup>. More recently, the Systolic Blood Pressure Intervention Trial (SPRINT)<sup>14</sup> showed that even in subjects 75 years and older, CVD outcomes and total mortality were reduced with intensive treatment as compared to the standard therapeutic strategies. However, similarly to HYVET, SPRINT was conducted in selected populations since they excluded the frailest subjects, those with clinically significant cognitive decline and dementia, those with several CVD and other co-morbidities, and patients living in NHs (Table 1).

**Table 1. Main exclusion criteria in HYVET and SRINT****Main Exclusion criteria in HYVET (1)**

Living in NHs  
 Limited autonomy  
 Clinical dementia  
 Heart failure needing treatment with ACEI, ARA, Diuretics  
 SBP < 140 mmHg in upright position  
 Renal failure  
 Patients presenting a high probability of having a major health problem during the 5 year follow-up period

**Main Exclusion criteria in SPRINT (3)**

Type 2 diabetes  
 History of stroke  
 Symptomatic heart failure within the past 6 months or reduced LVEF (<35%)  
 Clinical diagnosis of or treatment for dementia  
 Expected survival of less than 3 years  
 Unintentional weight loss (>10% of body weight) during the preceding 6 months  
 SBP of less than 110 mmHg following 1 minute of standing  
 Living in NHs

**Lack of evidence for treating in the very old frail subjects**

Indeed, very old frail people, with loss of autonomy, especially NH residents, have been systematically excluded from clinical trials on hypertension and most other chronic CV diseases<sup>15</sup>. Therefore, the effectiveness of new treatments, particularly medications for chronic diseases that typically affect older persons, is based on individuals who are healthier than average age-matched persons in the general population. When these new medications are used in older or frail persons, unexpected side effects commonly emerge. Very old frail people are not included in clinical trials primarily because they have multiple comorbid conditions (including cognitive impairment). Moreover, running clinical trials in NHs engender a higher level of difficulty related to:

- Multi-level decision-making (involvement of family members and others)
- Medical support not tailored to clinical research standards (poorly trained and small staff that is sporadically overseen by physicians)
- Increased administrative burden, (a high degree of regulation and concern about regulatory sanctions, and an abundance of required time-consuming documentation)

In these very frail people, we have data mainly from observational studies which show no or even an inverse relationship between BP and morbidity and mortality<sup>16</sup>. Some studies have indicated that in the very old, the relationship between BP and morbidity or mortality depends on the degree of frailty and functional decline<sup>17</sup>. In the more robust subjects the relationship is positive (the highest the SBP the highest the morbidity and the mortality), whereas in the most frail the relationship was the opposite.

The PARTAGE (Predictive values of blood pressure and ARterial stiffness in institutionalized very AGEd population) longitudinal study<sup>18</sup> was performed in 1,130 subjects  $\geq 80$  years living in NHs. These subjects were receiving at mean 7.1 drugs/day; 2/3 of them were under antihypertensive drugs (mean 2.2 drugs/day). The PARTAGE study showed an over-mortality in hypertensive subjects with low SBP (<130 mmHg) treated with 2 or more antihypertensive drugs. These individuals, who represented 20% of the total studied population, exhibited 80% increase in mortality compared to all other groups, even after adjustment for several comorbidities<sup>19</sup>. Similar results were recently observed by an Italian group in another population of older frail patients<sup>20</sup>. In that study a more pronounced cognitive decline was observed in patients who presented SBP levels <130 mmHg under antihypertensive treatment. Noteworthy, in these studies high levels of BP were not associated with increased morbidity or mortality as compared to those with normal-high values  $130 < \text{SBP} < 160$  mmHg.

Thus these contrasting results in very old hypertensive subjects are explained by the enormous functional heterogeneity among individuals of this age group and clearly show that functional status and biological age rather than chronological age should guide therapeutic strategies. Thus, the guidelines for robust older individuals cannot be extrapolated to very frail individuals, who have been completely excluded from the above-mentioned clinical trials.

Thus presently there are no evidence based guidelines on the goals of antihypertensive treatment in the very frail people living in NHs who:

- are a very rapidly increasing population
- have a very high (>75%) prevalence of hypertension.
- have been systematically excluded from all clinical trials in the field of hypertension
- present a clear over-mortality when low BP lev-

els are observed under several antihypertensive molecules.

In our opinion, the results of the PARTAGE and other studies make urgent to answer the question: Are many of these frail patients over-treated for hypertension, thereby increasing their morbidity-mortality?

### How to treat very old frail people with high BP?

A recent review paper by the coordinator and several partners of this proposal<sup>21</sup> concluded that there is limited evidence to support recommendations for hypertension treatment of frail, very old patients. This lack of evidence has been clearly recognized in an expert paper published by a joint committee of the European Societies of Geriatric Medicine (EUGMS) and Hypertension (ESH)<sup>22</sup>. The paper stated that controlled clinical trials, comparing different therapeutic strategies, will provide critical information to guide physicians how to treat hypertension in this venerable population.

Since such results are not available presently, this expert paper suggested to use a more personalized approach by taking into account the functional status and the level of frailty of the subjects.

The 2013 ESH/ESC guidelines<sup>8</sup> state that “in frail older patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and base them on monitoring of the clinical effects of treatment” In the recent expert paper we proposed that in these patients therapeutic decisions should be preceded by:

- accurate information on their functional capacity, cognitive status and, although its estimate in clinical practice is notoriously difficult,
- attention to multiple drug administration so common in this age stratum
- stratification of the frailty and autonomy status by one of the available rapid methods and
- identification and correction of factors that favour an excessive BP reduction, orthostatic hypotension, and other hypotensive episodes, such as concomitant treatments, malnutrition and dehydration.

The decision of the practicing physician to start treatment in a frail very old patient should be especially cautious (low drug doses and monotherapy) and to check patient status on a frequent basis (Table 2).

**Table 2. Management of people 80+ with diagnosis of hypertension**

- Frailty, autonomy status and multi-morbidity are major determinants for treatment strategies
- Treat all “robust” hypertensive subjects with SBP > 160 mmHg
- Target SBP 140-150 mmHg
- Start low (with one drug); Go slow
- Not more than 3 anti-hypertensive drugs
- In subjects with major frailty and loss of autonomy, consider reducing treatment if SBP < 130 mmHg even in the absence of side effects
- Check regularly (at least twice yearly) for orthostatic hypotension even in the absence of symptoms
- Check regularly renal function

Choice of antihypertensive drugs: The 2013 ESH/ESC guidelines<sup>8</sup> recommend all five major antihypertensive drug classes (with a preference for diuretics and calcium channel blockers in isolated systolic hypertension) for use in old hypertensive subjects, with no distinction between those above or below 80 years of age. In our recent expert paper<sup>22</sup>, we suggested that, based on the HYVET, in the 80+, ACE inhibitors and should be positioned at the same level as (thiazide and thiazide-like) diuretics and calcium channel blockers.

### Perspectives and Conclusions

Clearly, aggressive treatment of hypertension is justified in rather robust older subjects with the characteristics of the people enrolled in the clinical trials. However, this approach might be deleterious in very old frail people, with poly-medication, comorbidities, including loss of autonomy.

Presently, no clear recommendation exists regarding target SBP in the treatment of hypertension in very old frail subjects. Moreover, little is known about whether a SBP < 130 mmHg in these individuals in response to therapy increases rather than decreases morbidity and mortality. Controlled trials are necessary in the most frail subjects in order to obtain strong evidence for the benefits of the different therapeutic strategies.

In conclusion, it becomes clear that in the very old the “one size fits all” cannot be applied in the management of hypertension, due to the enormous functional heterogeneity in these people. We urgently need evidence-based precision medicine approaches to recommend actions to be carried out on patient management.

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