

RR An expert opinion from the ESH-EUGMS Working Group on the management of hypertension in very old, frail subjects

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Two years after the publication of the 2013 guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) (1), the ESH and the European Union Geriatric Medicine Society (EUGMS) have created a common working group in order to examine the management of hypertensive subjects over 80 years old. The general term “Hypertension in the elderly” is not sufficiently accurate since it mixes “younger” old patients (60-70 years) with the oldest old. Our group believes that the management of hypertension in individuals aged 80 years and older should be specifically addressed. Although arbitrary, this cut-off value identifies a population which is expanding faster than any other age group with a 50% increase of life expectancy during the past 50 years (2,3); furthermore, the incidence and prevalence of comorbidities, frailty and loss of autonomy greatly increases after the age of 80 years (4); finally, although there is limited evidence regarding the management of hypertension in this age group, the latest clinical studies indicate that in these patients treatment may not be the same as in patients in the lower age strata.

Aim of this Working Group was to discuss more in-depth a number of treatment aspects of hypertensive patients aged 80 years or older, with special focus on the difficulties and uncertainties posed by very old frail individuals. We focused, in particular, on the following points of the 2013 ESH/ESC guidelines

- Benefits of treatment
- Blood pressure (BP) thresholds and targets
- The choice of treatment

1- Benefits of treatment

The 2013 ESH/ESC guidelines (1), reported the results of the HYpertension in the Very Elderly double blind Trial (HYVET). This showed that in hypertensive patients aged 80 years

or more the administration of the thiazide-like diuretic indapamide supplemented, if necessary, by the ACE inhibitor perindopril led to a significant reduction in the risk of major cardiovascular events and all cause death compared to placebo (2). From this, the guidelines concluded that there is evidence that antihypertensive treatment is beneficial in octogenarians in whom BP is elevated, and that therefore BP lowering interventions can be strongly recommended within this age range. However, both the ESH/ESC guidelines (1) and other publications (5-8) also point out limitations in the demonstration that treatment is beneficial in octogenarians and this need to be addressed. First, the HYVET is thus far the only randomized clinical trial that has addressed this important issue, making confirmation by a second trial highly desirable. Second, the age of the HYVET patients was for the most part closer to 80 years (73% in the 80-84 and 22% in the 85-89 range), leaving the effect of treatment in patients close to or above 90 years of age largely unexplored. Third, because the trial was prematurely interrupted by the Safety Monitoring Board (due to the evidence of protective effect of BP reduction in the treated group) the follow-up was rather short (median 1.8 years). Despite the observation that in the HYVET patients the rate of events remained lower in the originally treated group one year after the trial termination (9), this requires the duration of benefit to be determined. Finally, the 2013 ESH/ESC guidelines state that '*the HYVET deliberately recruited patients in good physical and mental conditions and excluded ill and frail individuals, who are common among octogenarians, and also excluded patients with clinically relevant orthostatic hypotension*' (1), thereby emphasizing probably the most important limitation of the available information, i.e. leaving out of consideration the influence of patients' general health, concomitant medication and frailty on the decision about antihypertensive treatment implementation.

Post hoc analysis of the HYVET trial did not find a relationship between the benefit of antihypertensive treatment and patients' frailty (10). This is reassuring for community-

dwelling older hypertensives but it is worth remembering that the HYVET did not include very frail patients and that patients with multiple morbidities and clinically significant cognitive impairment were also excluded. Indeed, both recent observational studies and registries show an important influence of the frailty status on the relationship between BP and outcomes, especially in treated hypertensives. This can be exemplified by studies that show the association between BP and mortality to vary according to the walking speed (11), cognitive function, assessed with the mini mental state examination (MMSE) and disability, measured using the activity of daily living (ADL) (12)- Indeed, Odden et al (11) showed that, systolic BP in faster walkers was positively correlated with mortality, while no relationship between BP and mortality was observed among slower walkers. Moreover, in patients unable to complete the walk test BP was negatively associated with the risk of death (6). In the Milan Geriatrics study (12), higher systolic BP values were related to lower mortality among individuals aged 75 years or older who had an impaired MMSE (< 25 points) or ADL (<6 points). Also, the Predictive Value of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population (PARTAGE) study has shown that what applies to middle-aged persons does not necessarily apply to old (≥ 80 years) nursing home residents (13-15), i.e. the frailest oldest patients. Actually, in this very old frail population, values of BP recorded with clinical standard procedures were very similar to those obtained with multiple 3-day morning and evening measurements » (13) and the negative relationship between the main endpoint of the study (total mortality and major CV events) and SBP was observed with BP measured by a clinician, or self-measured (14). Interestingly, in this study the highest mortality rate was observed in patients with systolic BP less than 130 mmHg, who were treated with two or more antihypertensive drugs, at variance from what was seen in those treated with one antihypertensive agent or not receiving any antihypertensive drug at all (15). Likewise, Mossello et al (16) found a more pronounced cognitive decline in treated old

hypertensive patients suffering from mild cognitive impairment or dementia in whom systolic BP was low (< 128 mmHg). Such an effect was not observed in subjects with low systolic BP but without antihypertensive treatment.

It is important to remember that both low BP and orthostatic hypotension are associated with syncope, falls and related injuries and fractures (17-19). Therefore, both the benefits (including preserving autonomy) and the risks of antihypertensive therapy should be considered before starting treatment in the very frail older population. This population is the one at the highest risk of hypertension-related cardiovascular events, but also of hypotension-related events (19-21). Hypotension-related events are likely to be more common in real life than in clinical trials in which treatment is delivered by expert physicians and patients are followed closely. In a recent analysis of a large real-life database very old individuals showed a significant increase in hospitalizations for hip fracture over the 30 days after initiation of antihypertensive drug treatment (22). This has been previously observed in patients with a mean age of 80 years (26% between 86 and 100) over the 45 days after antihypertensive treatment initiation (23).

2- BP thresholds and targets

Because in the HYVET, patients were recruited if their entry systolic BP was ≥ 160 mmHg, this is the systolic BP value recommended by the 2013 ESH/ESC guidelines at which drug treatment in octogenarians should be started (1). The threshold for treatment has been set at a lower systolic BP level (≥ 150 mmHg) in the US 2014 guidelines (5) but because octogenarians with entry systolic BP values < 160 mmHg have never been studied in randomized clinical trials nor shown to have beneficial effects of BP lowering interventions in subgroup data from trials addressing a larger age range, this does not appear to be based on solid evidence. It remains thus unsubstantiated whether in this very old patient category grade

1 hypertension, i.e. a systolic BP between 140 and 159 mmHg, might benefit from antihypertensive drugs.

Evidence on the BP goals for treatment in octogenarians is also limited. Both the 2013 ESH/ESC (1) and the US guidelines (5) recommend adopting the goal set by the HYVET, i.e. < 150 mmHg systolic BP but neither addresses the question of the systolic BP value below which the treatment may interfere with patients' safety. This is a critical issue because, as mentioned above, i) observational studies have repeatedly shown that in the very old population low BP values are associated with an increased morbidity and mortality ii), somewhat statistically underpowered, randomized Japanese trials have not found clear benefits of systolic BP reductions below 140 mmHg (24, 25) and iii) a systolic BP reduction to <120, 130 or even 140 mmHg may be associated with an increased risk of negative outcomes, i.e. a J curve phenomenon that appeared to be especially evident in frail individuals. Although the possibility of reverse causality (i.e. greater initial risk as the cause of an excessive BP fall and increased outcomes) cannot be excluded, a pathophysiologically founded hypothesis is that in frail very old subjects an impairment of the mechanisms preserving perfusion might critically decrease blood flow to vital organs (heart, brain, kidney) (21). This is at variance from healthier old individuals in whom no clear negative influence of blood pressure decrease on vital organ perfusion and associated complications has been reported (26, 27). Therefore, the following multiple questions still remain open. Do frail very old hypertensives get benefits from antihypertensive treatment? Is the benefit similar or different in non-frail and frail individuals? Should the BP threshold at which to start treatment be higher as recently recommended by guidelines? Which are the BP targets that maximize protection in frail very old patients, without posing a risk to their safety?

The recently published Systolic Blood Pressure Intervention Trial (SPRINT) (28) shows that among patients at high cardiovascular risk and already using antihypertensive drugs targeting

a systolic BP of 120 mmHg resulted in lower incidence of major cardiovascular events and death from any cause compared to patients targeting a systolic BP of 140 mmHg; this result was also statistically significant in the subgroup (28% of all) of patients more than 75 years old. However, in the SPRINT the number of patients aged 80 years or older has not been reported and may be substantially lower than the 28% (2600) patients aged 75 years or older.. Furthermore, interpretation of several aspects of the SPRINT data (lack of beneficial effect on stroke, masking effect of diuretics on signs and symptoms of more than three drug heart failure, blood pressure measuring approach, etc) are still under discussion (29,30). Finally, and more importantly, in patients with advanced frailty, cognitive decline, loss of autonomy and living in nursing home were excluded from the trial. Exclusion from trial extended to patients with decompensated heart failure, history of stroke and diabetes, i.e. conditions very commonly associated with hypertension in very aged individuals in whom they represent a common cause of death. This is a crucial issue also because in SPRINT, the aggressively treated group showed a substantial increase of hypotension, syncope, electrolyte abnormalities and renal failure, i.e. adverse reactions that are likely to be magnified in very old patients, even more so if frail. Thus, application of the SPRINT results in this population cannot be done unconditionally, also considering that other studies including frail people have not obtained similar results. While potentially useful to robust old hypertensives, these results may have a limited transferability to frail, very old patients in whom the treatment strategies and the treatment goals should be largely driven by their functional status and comorbidities.

3- Choice of treatment

Based on trials performed in patients aged 60 years or more both the 2013 ESH/ESC (1) guidelines and the US guidelines (2) recommend the antihypertensive treatment to be implemented in old hypertensive subjects to use the same drug classes that are recommended for younger patients, i.e. diuretics, angiotensin receptor antagonists, ACE inhibitors and

calcium channel blockers, with an extension to beta-blockers in the ESH/ESC guidelines (1). Based on large meta-analyses they also consider the above 5 classes similarly protective in old hypertensive individuals, although indicating diuretics and calcium channel blockers as the preferred choice in isolated systolic hypertension given the preferential use of these two drugs in trials on this condition. Neither the European nor the United States guidelines mention any difference in the type of treatment in hypertensive patients aged 80 years or more compared to patients below 80 years. In the HYVET the drugs employed were the thiazide-like diuretic indapamide complemented by perindopril in about 70% of the patients, suggesting a possible preference for a treatment based on a diuretic-ACE inhibitor combination. However, in a pre-specified secondary analysis of a Japanese study (31) on hypertensive patients aged 75-84 years, those receiving an angiotensin receptor antagonist/calcium channel blocker combination showed a reduction in the risk of stroke compared to patients receiving an angiotensin receptor antagonist/diuretic combination. Given the evidence that the benefit of treatment largely depends on BP lowering per se (32), i.e. regardless how it is obtained, the opinion of this Working Group is that in principle the large number of antihypertensive drug classes recommended for younger age strata are suitable for use also in the oldest-old individuals. Except when required for specific clinical conditions (e.g. angina pectoris, previous myocardial infarction and heart failure), use of beta-blockers in these very old hypertensive individuals remains controversial, however (33,34).

In the 2013 ESH/ESC guidelines (1) the suggestion is made to consider initiation of antihypertensive treatment with a 2-drug combination if cardiovascular risk is high, with no distinction between younger and older patients. However, in octogenarians, initial administration of two antihypertensive drugs, even when administered at low doses, may put subjects at an unwarranted risk of hypotension, given that homeostatic mechanisms that maintain BP against gravity and other challenges undergo a progressive impairment as age

advances (35). Furthermore, increasing the number of the prescribed drugs may increase the probability of adverse drug, drug-drug and drug-disease reactions and interactions in patients in whom polypharmacy is extremely common due to the frequent concomitance of both cardiovascular and non-cardiovascular diseases (36,37). Finally, an increased number of prescribed drugs is known to have a negative effect on adherence to treatment, an especially serious problem in very old patients in whom adherence (and errors in taking the prescribed medicines) may be adversely affected by cognitive dysfunction and dementia (38). Combination of two antihypertensive drugs should be considered if monotherapy fails to control BP, but only if consideration of the potential protective effect of BP reduction versus the risk of hypotension and other adverse effects makes a benefit likely. As already mentioned in the 2013 ESH/ESC (1) and other guidelines (8), antihypertensive treatment in octogenarians should in general not exceed 3 different medications, unless BP remains severely uncontrolled, or patients become 80 under an earlier initiated more than three drug regime, but still well-tolerated, treatment. Under these circumstances, however, patients' follow-up should be intensified because a large body of evidence shows that drug-to-drug interactions and other iatrogenic problems dramatically increase with an increase in the number of administered drugs and more so in frail patients (39)

Suggestions of the Working Group for the management of hypertension in octogenarians.

Based on the above comments, we propose the following:

a- Treatment initiation: The 2013 ESH/ESC guidelines state that in individuals aged 80 years or older with an initial systolic BP ≥ 160 mmHg, systolic BP should be reduced by drug treatment provided that patients are in good physical and mental conditions. We believe that this recommendation should be accompanied by 1) a more precise definition of the meaning

of the term “good physical and mental conditions” and 2) an indication of how physical conditions, mental conditions and the frailty status can be assessed.

A rapid (<10 minutes) assessment of frailty is feasible. The most frequently employed is the Fried frailty phenotype (40) in which frailty is defined by the presence of at least 3 of the following: weight loss, exhaustion, weakness, decreased gait speed, and diminished physical activity. Other scales used in different countries (41-43) may also be referred to.

The ESH/ESC guidelines also state, that “continuation of a well tolerated antihypertensive treatment should be considered when a treated individual becomes octogenarian”. This is a reasonable recommendation, but we suggest that in this case physicians are advised to monitor the frailty status in order to detect when a change in treatment strategy may be needed.

b- Treatment goals: The 2013 ESH/ESC guidelines recommend treatment to lower systolic BP to < 150 mmHg in octogenarians in good physical and mental conditions. We believe that this might be usefully complemented by mentioning that, while keeping <150 mmHg systolic BP as the evidence-based target, for safety reasons antihypertensive drugs should be reduced or even stopped if systolic BP is lowered to <130 mmHg, thus keeping the 150 to 130 mmHg on-treatment systolic BP values as a safety range. Self-assessment of BP at home and if necessary 24 h ambulatory BP measurements can contribute to identify treated patients with too low BP levels. Some consideration should also be given to the assessment of subclinical organ damage in particular, systolic and diastolic dysfunction as well as arterial stiffness. However the question is raised, concerning the prognostic significance of these parameters in older hypertensives, and whether their improvement would actually translate into an improvement in mortality in the elderly. (44). It should be emphasized that nearly all guidelines on BP targets refer to office BP values because no outcome trial has addressed the optimal out-of-office BP target in older or younger hypertensive patient strata. To date, what

has been established is that 1) office BP is higher than 24-h mean or home BP (45) and 2) this discrepancy decreases progressively as office BP decreases. This suggests that these values do not differ substantially in individuals with office BP controlled (46), a possibility, however, that needs to be tested by randomized trials.

c- Choice of antihypertensive drugs: The 2013 ESH/ESC guidelines (1) 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. We suggest that a distinction should be made and that, based on the HYVET, in octogenarians, ACE inhibitors and thiazide-like diuretics should be positioned at the same level as calcium channel blockers. The working group thinks that despite the age-related high cardiovascular risk, initial high dose or combination treatment should not be encouraged, and that combination treatment should only be considered after failure of initial low dose therapy.

d- Frail very old patients (people living in nursing homes or needing assistance on a daily basis for their basic activities): The 2013 ESH/ESC guidelines 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” We suggest that in these patients therapeutic decisions should be preceded by 1) accurate information on their functional capacity, cognitive status. Although notoriously difficult, an estimate of patient’s prognosis should also be attempted; 2) attention to multiple drug administration so common in this age stratum; 3) stratification of the frailty status by one of the available rapid methods; and 4) identification and correction of factors that predispose to 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

It is obvious that the recommendations of our group pertain mainly to very old people (i.e. 80 year or over) with frailty. However, we believe that an individual in his late sixties or early seventies who expresses the condition of frailty - and in whom at that moment a difference between the calendar and the biological age becomes apparent- should be approached in a similar way. Since prevalence of frailty dramatically increases with increasing age (47), the latter situation however would take place in few cases. For this reasons, a systematic screening for frailty, which we propose for very old people, might take place in their younger counterparts only when a clinical and functional problems become imminent.

Finally, we would like to point out that research based on registries, administrative databases but also interventional controlled trials should be favoured to assess the benefits/risks ratio of multi-drug antihypertensive treatment in the growing population of very old frail patients.

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