

# Compendium on the Pathophysiology and Treatment of Hypertension

## Hypertension Management in Older and Frail Older Patients

Athanase Benetos, Mirko Petrovic, Timo Strandberg

**Abstract:** The prevalence of arterial hypertension, particularly systolic hypertension, is constantly rising worldwide. This is mainly the clinical expression of arterial stiffening as a result of the population's aging. Chronic elevation in blood pressure represents a major risk factor not only for cardiovascular morbidity and mortality but also for cognitive decline and loss of autonomy later in life. Clinical evidence obtained in community-dwelling older people with few comorbidities and preserved autonomy supports the beneficial effects of lowering blood pressure in older hypertensive subjects even after the age of 80 years. However, observational studies in frail older individuals treated for hypertension have shown higher morbidity and mortality rates compared with those with lower blood pressure levels. Clearly, in very old subjects, the therapeutic strategy of one size fits all cannot be applied because of the enormous functional heterogeneity in these individuals. Geriatric medicine proposes taking into account the function/frailty/autonomy status of older people. In the present review, we propose to adapt the antihypertensive treatment using an easy-to-apply visual numeric scale allowing the identification of 3 different patient profiles according to the functional status and autonomy for activities of daily living. For the preserved function profile, strategies should be those proposed for younger old adults. For the loss of function/preserved activities of daily living' profile, a more detailed geriatric assessment is needed to define the benefit/risk balance as well as requirements for the tailoring of the various therapeutic strategies. Lastly, for the loss of function and altered activities of daily living' profile, therapeutic strategies should be thoroughly reassessed, including deprescribing (when considered appropriate). In the near future, controlled trials are necessary for the most frail older subjects (ie, in those systematically excluded from previous clinical trials) to gain stronger evidence regarding the benefits of the various therapeutic strategies. (*Circ Res.* 2019;124:1045-1060. DOI: 10.1161/CIRCRESAHA.118.313236.)

**Key Words:** activities of daily living ■ aging ■ blood pressure ■ frailty ■ hypertension

### Demographics and Epidemiological Aspects of Arterial Hypertension in the Very Old

The prevalence of arterial hypertension is constantly rising, mainly as the result of the aging of the population, in particular, the increase in the population over 80 years old, which has expanded exponentially over the past 40 years.<sup>1</sup> Currently, the life expectancy for those 80 years and over living in the OECD (Organisation of Economic Cooperation and Development) group of countries is ≈9 years compared with about 6 years in the 1970s, representing an increase of 50%.<sup>2</sup> In the European Union, there were 27.3 million people aged 80 years and older in 2016 (5.4% of the total population) versus 20 million in 2006 (4.6% of the total population).<sup>3</sup> In the United States, the percentage of people of 80 years and older is projected to be 7.4% in 2050,<sup>4</sup> which is exactly double the percentage observed in 2010. These demographic changes explain why, despite the fact that the incidence of hypertension at a given age has changed very little,<sup>5</sup> the absolute number of individuals with hypertension is constantly growing.

Observational data from the Framingham Study suggest that the lifetime risk of developing hypertension is >90% for an individual aged 55 to 65 years.<sup>6</sup> Thus, the continuously increasing number of older individuals ultimately leads to a growing population with high blood pressure (BP). In addition, the aforementioned demographic changes concomitantly lead to a greater number of older people in need of both home and institutionalized care because of cognitive and functional decline, frailty, multimorbidity, polypharmacy, as well as partial or complete loss of autonomy.<sup>7,8</sup>

Indeed, the number of very old individuals exhibiting frailty (ie, a state of vulnerability to poor resolution of homeostasis after a stressor event and a consequence of cumulative decline in many physiological systems during a lifetime),<sup>9</sup> loss of autonomy, and limited life expectancy have dramatically increased worldwide. In European countries, the number of people living in nursing homes (NHs) has increased sharply over the past decade<sup>10</sup> such that, in 2013, there were 3.7 million long-term care beds in nursing and residential care

From the Department of Geriatrics and FHU CARTAGE, CHU de Nancy and INSERM 1116, Université de Lorraine, France (A.B.); Department of Geriatrics, Ghent University Hospital, and Ghent University, Belgium (M.P.); University of Helsinki, Clinicum, and Helsinki University Hospital, Finland (T.S.); and Center for Life Course Health Research, University of Oulu, Finland (T.S.).

Correspondence to Athanase Benetos, MD, PhD, Department of Geriatrics, University Hospital of Nancy, 54511 Vandoeuvre les Nancy, France. Email a.benetos@chru-nancy.fr

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**Nonstandard Abbreviations and Acronyms**

<b>ADL</b>	activities of daily living
<b>BP</b>	blood pressure
<b>CGA</b>	comprehensive geriatric assessment
<b>CSHA</b>	Canadian Study of Health and Ageing
<b>DBP</b>	diastolic blood pressure
<b>HYVET</b>	Hypertension in the Very Elderly Trial
<b>IADL</b>	instrumental activities of daily living
<b>NH</b>	nursing home
<b>PP</b>	pulse pressure
<b>SBP</b>	systolic blood pressure
<b>SPRINT</b>	Systolic Blood Pressure Intervention Trial

facilities in the European Union, with the number of beds constantly increasing. For example, between 2011 and 2014, the number of NH beds in France increased from ≈611 000 to 634 500 and from 220 000 to 234 000 beds in Italy. In addition to those living in NHs, and partly because of a saturation of the capacity of institutionalized care, many community-dwelling older people have advanced frailty with limited autonomy; these individuals also require assistance for basic daily activities. For instance, data from the French National Institute of Statistics and Economic Studies<sup>11</sup> show that among individuals aged 80 and over, 650 000 live in the community and receive Autonomy Personalized Allocation, in addition to the 600 000 who live in NHs. Thus, in France one-third of the total 80+ population (1.25 out of 3.80 million people) present a significant loss of autonomy with consequently increased need for permanent assistance in activities of the daily living.

Of greater issue is the fact that loss of autonomy, living in an NH, or significant cognitive decline are constant exclusion criteria (or lead to refusal) in clinical trials studying the clinical interest of medications for chronic diseases.<sup>12</sup> Data from France and Italy show that >80% of NH residents have a diagnosis of arterial hypertension, over 80% of who receive antihypertensive medication.<sup>13</sup> However, very old frail people are not included in randomized controlled trials (RCTs) primarily because they have limited autonomy, multiple comorbid conditions (including cognitive impairment), thus leading to refusals and difficulties in analyses because of competitive mortality. Placebo-controlled studies are moreover particularly difficult, given that a change in existing treatment may not be ethically acceptable. Furthermore, running RCTs in NHs creates a higher level of difficulty related to<sup>14</sup>

- Multilevel decision-making (involvement of family members and others).
- Medical support not tailored to clinical research standards (small and poorly trained 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).

Given the lack of trials that have included older patients with the aforementioned severe frailty and decreased autonomy profile, the benefit/risk ratio of antihypertensive treatment

(as well as treatment of several other chronic diseases that affect older people), is thus primarily based on evidence obtained in individuals who are more robust, mildly/moderately frail at most, present fewer comorbidities, and receive less medication.

Simply stated, very old frail people who reside in NHs are usually prescribed medications, the benefits of which are based on research in younger and healthier populations. This is of particular concern for the treatment of arterial hypertension, one of the most common conditions in older adults. There is evidence that for general older populations with chronic conditions and cardiovascular drug treatment (Medicare beneficiaries), survival does not necessarily differ from that observed in RCTs.<sup>15</sup> However, with an older patient, it often happens that medication, once appropriately initiated, is not routinely reevaluated in conditions of a deteriorating cognitive and functional state and a decreasing life expectancy. Therefore, in older patients presenting advanced or terminal disease, dementia, severe frailty or full dependence, and those receiving high-risk drugs or combinations thereof, the meticulous tailoring of pharmacotherapy—even including deprescribing (see below)—should be considered.<sup>16,17</sup>

### Changes in BP During the Aging Process: the Role of Arterial Stiffness and Comorbidities

#### Increase in Systolic BP and Decrease in Diastolic BP With Age

Arterial stiffness is the major cause of elevated systolic BP (SBP) and pulse pressure (PP, SBP minus diastolic BP [DBP]) as well as lower DBP in older adults. Moreover, these BP age-related alterations are powerful determinants of major cardiovascular disease (CVD) events and all-cause mortality.<sup>18–20</sup>

Until the age of 50 to 60 years, both SBP and DBP increase with age. Over the age of 60 years, in the majority of cases, SBP increases with age, whereas DBP concomitantly remains stable or even decreases spontaneously. The most common cause for the disruption of the correlation between SBP and DBP—leading to an excessive increase in PP—is the progressive stiffening of the arterial wall.<sup>18,19</sup> Indeed, arterial stiffness arises as a consequence of several structural and functional changes of the large arteries. Wall hypertrophy, calcifications, and atheromatous lesions, as well as changes in the extracellular matrix (such as an increase in collagen and fibronectin, fragmentation and disorganization of the elastin network, nonenzymatic crosslinks and cell-matrix interactions), are the main structural determinants of the decrease in elastic properties and the development of large artery stiffness.<sup>20</sup> In addition, functional changes, such as impaired vascular endothelial function and modification of smooth muscle cell reactivity, contribute to the stiffening of the arterial wall.

It should be emphasized that SBP is dependent on both left ventricular performance and on stiffness of the aorta and other large arteries.<sup>18,21</sup> As a result, peak systolic pressure will be greater if the arterial wall is more rigid. However, after closure of the aortic valves, arterial pressure gradually falls as blood is drained to the peripheral vascular networks. The

minimum diastolic pressure is determined by the duration of the diastolic interval and the rate at which the pressure falls. The rate of fall in pressure is influenced by peripheral resistance and by the visco-elastic properties of the arterial wall. At a given vascular resistance, the fall in diastolic pressure will be greater if large artery stiffness is augmented. The visco-elastic properties of arterial walls are also a determinant of the speed of propagation of the arterial pressure wave (pulse wave velocity) and of the timing of wave reflections. Thus, stiffening of the arteries increases pulse wave velocity and may be responsible for an earlier return of the reflected waves, which is superimposed to the incident pressure wave, thereby further contributing to the increase in SBP and PP.<sup>21</sup>

### Impaired BP Homeostasis and Increased BP Variability

Postural as well as other BP variations increases in older adults. Orthostatic hypotension is the most common expression of these variations and is considered as a risk factor for cardiovascular and noncardiovascular morbidity and mortality.<sup>22</sup> Orthostatic hypotension is related to several chronic diseases: hypertension, chronic autonomic failure in the context of Parkinson disease and other neurological diseases, polyneuropathy mainly in the context of diabetes mellitus. Nonneurogenic orthostatic hypotension is largely attributable to several conditions often observed in older adults, namely dehydration and polypharmacy (especially in case of vasodilators, diuretics, and psychotropic medications).<sup>23</sup>

In addition, the presence of large artery stiffness leads to impaired activation of the baroreflex<sup>24</sup> and inappropriate BP/heart rate response to postural changes.<sup>25</sup> Several studies have shown that stiffer large arteries contribute to greater BP variability during orthostatic reactions inducing both orthostatic hypotension<sup>26</sup> and orthostatic hypertension.<sup>27</sup>

Arterial stiffness is also implicated in the increased variability in BP observed in several other conditions, such as exercise,<sup>28</sup> postprandial BP variations (both increase and decrease in BP are exaggerated in individuals with pronounced arterial stiffness),<sup>29</sup> and between-visit BP variability.<sup>25</sup> These observations indicate that large artery stiffness contributes to inappropriate homeostatic mechanisms responsible for maintaining

both BP and tissue perfusion stability during various physiological conditions.

Modifications in orthostatic BP have been shown to affect the prognosis of older people<sup>30,31</sup> by increasing the risk of syncope and falls, leading to hospitalization and functional impairment,<sup>32,33</sup> in addition to increasing CVD and all-cause mortality.<sup>31,34</sup> Somewhat paradoxically, orthostatic reactions may be alleviated with better hypertension control.<sup>35</sup>

Although the complications of orthostatic hypotension are well known, a growing number of clinical studies indicate that an increase in BP in the upright position (orthostatic hypertension) is also an independent risk factor of cerebrovascular disease<sup>36–38</sup> and other target organ damage.<sup>37–39</sup> A prospective study showed that orthostatic hypertension was associated with a higher risk of developing hypertension later in life.<sup>40</sup>

We have moreover recently reported that orthostatic hypertension in very old subjects living in NHs was related to an increased risk of CVD morbidity/mortality in a manner similar to that observed with orthostatic hypotension.<sup>30</sup>

### Impact of High BP Values in Older Subjects

#### Respective Roles of SBP, DBP, and PP

SBP and PP are better indicators of CVD risk in older subjects, whereas in younger subjects, DBP is a better reflection of CVD risk.<sup>41,42</sup> The age-dependent changes in the prognostic value of BP levels are related to the age-related modifications of SBP and DBP, as presented in the previous section. DBP in young patients is primarily dependent on peripheral resistance, and therefore low DBP is a reflection of low peripheral resistance. Moreover, in young subjects with hyperkinetic circulation, DBP is less variable than SBP, thus better-reflecting CVD risk. In older subjects, a low DBP mainly reflects high arterial stiffness, which is a major manifestation of arterial aging rather than low peripheral resistance (Table 1).<sup>18,19,21</sup> In this instance, low DBP is associated with high SBP/PP values and increased CVD risk. The clinical application of these considerations is that, in people older than 55 to 60 years, SBP is a much more important CVD risk factor than DBP.<sup>43</sup> All of the recent guidelines highlight that, in older adults, SBP seems to be a better predictor of events than DBP.<sup>44</sup> Moreover, PP can

**Table 1.** Schematic Representation of the Various BP Profiles in Older Subjects

Age, y	SBP	DBP	BP Regulation Physiopathology	Main Risks	Better BP Risk Marker	Management
65–80	↑↑	↑	High PR and AS	CV complications, cognitive decline	High SBP	Physical activities, assess TOD and global CVR, medical tt (SBP <140)
65–80	↑	↔↓	High AS	CV complications, cognitive decline	High SBP, PP, low DBP	Physical activities, assess TOD and global CVR, medical tt (SBP <140)
>80	↑↑	↔↓	High AS	CV complications, falls	High PP, low DBP, OH	CGA, medical tt (SBP <150 or SBP <140 according functional status)
>80	↔↓	↓↔	High AS and comorbidities	CV complications, falls, loss of autonomy	Normal/low SBP, low DBP; normal/high PP, OH	CGA, deprescribing if SBP <130 or OH, fight polypharmacy

AS indicates arterial stiffness; BP, blood pressure; CGA, Comprehensive Geriatric Assessment; CV, cardiovascular; CVR, cardiovascular risk; DBP, diastolic blood pressure; OH, orthostatic hypertension; PP, pulse pressure; PR, peripheral resistance; SBP, systolic blood pressure; TOD, target organ damage; and tt, treatment.

have an additional prognostic value in individuals aged over 65 to 70 years reflecting the fact that, in older adults, a high SBP carries a greater risk when associated with a low DBP.<sup>45</sup> Finally, for reasons developed later in this article, in very old, frail, multimorbid subjects, SBP also becomes less informative for the definition of CVD risk.

### High BP and Cardiovascular Complications

Several large population studies have indicated that the higher the office BP, the higher the risk of stroke and coronary heart disease, sudden death, heart failure, peripheral artery disease, and end-stage renal disease. Although some studies suggest that BP has limited predictive value for total mortality after the age of 70 years,<sup>46</sup> large epidemiological studies have shown that the associations between BP and CVD events are observed in the majority of subjects aged over 80 years.<sup>47</sup> However, although for the general population the relationship with BP extends from high BP levels to relatively low values (110–115 mm Hg for SBP and 70–75 mm Hg for DBP), in older populations, these lower thresholds are variable depending on the age and functional status of the studied subjects. A continuous relationship with events is also exhibited by out-of-office BP values, such as those obtained by ambulatory BP measurements and home BP measurements.

Metabolic risk factors are more common when BP is high than when BP is low.<sup>48,49</sup> However, particularly in older subjects aged over 80 years, the role of certain metabolic factors, notably dyslipidemia, is much less established.<sup>50</sup> This does not exclude, however, that treatment of dyslipidemia may be beneficial, although RCTs proving or disproving the latter are currently lacking.<sup>51</sup>

### Impact of Hypertension on Neurocognitive Performance

Observational studies have documented an association between elevated BP in middle age and the risk of cognitive impairment. This relationship was observed for the first time in the Framingham study in which a high BP detected 20 years earlier was inversely associated with cognitive performance among untreated hypertensive subjects.<sup>52</sup> Since this initial observation, most epidemiological studies have confirmed this relationship between hypertension and cognitive decline.<sup>53</sup> For example, the Honolulu-Asia Aging Study which followed 3735 subjects for over 30 years showed that the risk of cognitive decline at age 78 increased with the level of BP measured 25 years earlier.<sup>54</sup> In a seminal study in the field, Skoog et al<sup>55</sup> showed that over a follow-up period of 10 to 15 years, patients with hypertension developed dementia more frequently than normotensive subjects. On an even shorter follow-up period of 4 years, the Epidemiology of Vascular Aging study found the risk of cognitive decline to be multiplied by 6 among patients with untreated chronic hypertension compared to a normotensive group.<sup>56</sup> However, such relationship between BP levels and cognitive decline in older populations was not observed in other clinical studies.<sup>57</sup> Hypertension duration, testing methods, as well as differences in the tested population may explain these discrepancies. In addition, the current concept is that midlife BP level is more important as a risk factor for

late-life cognitive impairment and dementia than BP levels assessed in late-life.<sup>58</sup>

The relative failure of antihypertensive treatments in preventing neurocognitive diseases observed in clinical trials in older hypertensive subjects is likely because of the relative short duration and late onset of these studies.<sup>53,59,60</sup> In fact, although a reduction in BP levels can be achieved with antihypertensive therapy, vascular and cerebral alterations caused in part by long-term hypertension precede treatment and thus cannot be reversed by such intervention. This hypothesis may also explain why in several studies, markers of arterial aging can potentially identify subjects at higher risk of cognitive decline, whereas BP levels alone do not seem to have a significant predictive value.<sup>61–63</sup> Finally, recent epidemiological data from the Framingham study report a strong reduction in the incidence of neurocognitive syndromes between 1977 and 2008, with one of the more plausible explanations of this observation being the improvement in BP control in the population, especially in middle-aged hypertensive subjects.<sup>64</sup>

### BP and Reverse Causality

Several studies have challenged the classical association between hypertension and CVD or all-cause mortality in the very old and even observed inverse associations between both systolic and DBP and mortality.<sup>65–68</sup> A decline in BP over time in older subjects with hypertension is common and has even been observed in the control group of the HYVET (Hypertension in the Very Elderly Trial) as well as being associated with increased mortality.<sup>69,70</sup> BP may also decrease in these subjects as a result of cardiovascular and neurological comorbidities, loss of weight, dehydration, as well as polypharmacy. Irrespective of the underlying mechanism(s), whereas a decreasing BP is a marker of declining health, a high BP may conversely become a marker of good health in a phenomenon of reverse causality. In the presence of arterial stiffness, declining BP may further decrease an already low DBP, which in turn leads to lower coronary perfusion.<sup>71</sup> Thus, the issues of reverse causality confound the risk stratification according to BP levels. Alternative approaches for the estimation of CVD risk in these subjects—such as direct measurements of functional arterial characteristics (pulse wave velocity, PP amplification, endothelial function, etc)—may indeed provide better information.<sup>13,72</sup> The progressive decline in BP over time in older patients also suggests that the requirements for antihypertensive treatment may decrease over time.

Interestingly, in very old frail subjects, several recent observational studies have shown that low SBP levels (SBP <130 mm Hg) were associated with higher morbidity and mortality rates in those receiving BP-lowering drugs but not in those with spontaneously (non-drug-related) BP levels.<sup>73–76</sup> These observational findings may be because of reverse causality because having BP-lowering medication in old age probably reflects longer hypertension history with its consequences during life-course and, therefore, higher mortality risk than among people without medication. Another interpretation is that the medication-related decrease in BP in these very frail individuals could worsen – not improve – the prognosis. Although empirical support is lacking,<sup>53,60</sup> we hypothesize

that, in the presence of severe frailty, altered circulatory autoregulation may cause tissue hypo-perfusion in instances of a significant drop in BP due to multiple antihypertensive drugs. Thus, in these individuals, an SBP <130 mmHg in response to therapy might increase rather than decrease morbidity and mortality.<sup>77</sup>

High BP in older people is a complex and heterogeneous condition. When attempting to establish evidence-based on-treatment BP targets, it becomes obvious that one size does not fit all.<sup>78</sup> Therefore, strategies to verify the appropriateness and relevance of a given treatment over time during the course of changes in a patient's status are welcome. For the time being, considering BP targets—thereby including individually adjusted upward when indicated—is probably the best means to avoid overtreatment not only at the initiation of therapy but also during follow-up.

### Clinical Evaluation of Older Adults With Hypertension

In old subjects with suspected hypertension, a thorough history, physical examination, and a limited number of selected laboratory and complementary exams should be performed. The aim of these exams is 2-fold:

1. Answer the classical questions as for every subject with a new onset of hypertension, that is, confirm the presence of a permanent BP elevation, exclude a secondary hypertension and evaluate the global CVD risk.
2. Assess the global functional status of the subject (comorbidities, all medications, frailty, and autonomy).

### Specificities of the Clinical Evaluation in Older Adults With Hypertension

Evaluation of patients >80 years usually differs from a standard medical evaluation. First and foremost, physicians must take into account that managing old patients is highly time-consuming because of several factors: complexity of the health condition because of multiple comorbidities, physical and cognitive slowness of older people, and the fact that most of the time, old frail subjects are accompanied by family members and professional caregivers with whom physicians have to discuss several issues.<sup>79</sup> For very old patients, especially those who are frail, history-taking and physical examination might have to be done at different times, and physical examination might even require 2 sessions because patients become exhausted.<sup>80</sup>

The diagnosis of hypertension should be based on at least 3 different BP measurements, taken on 2 separate office visits. The rules of office BP measurements are the same as for younger individuals. One specific point is the necessity of having, in addition to regular size and overweight cuffs, child-size cuffs for those older individuals with very low body mass index.

Generally, BP should be measured in sitting position. To assess orthostatic reaction, BP should be measured first in supine followed by upright position. This is particularly important to perform before any start of treatment and before any change in treatment. The measurements should be confirmed by home self-measurements to better assess BP levels and eliminate white coat reactions. Although informative, 24-hour

ambulatory BP measurements are of limited interest in very old patients and not always very well tolerated.<sup>81</sup> The main interest of these measurements is the detection of possible relationships between BP levels and symptoms, especially in treated hypertensive subjects

Secondary (potentially curable) hypertension needing a specific therapeutic intervention is not a very frequently encountered situation in older hypertensive patients. Therefore, it might be less useful for the older patient and less cost-effective to perform an extensive workup for the majority of older patients with hypertension.<sup>82,83</sup> Symptoms associated with high BP, especially certain typical symptoms of secondary hypertension observed in younger hypertensive subjects, are much less frequent and less specific in older individuals, primarily because of the presence of multiple comorbidities. However, when an older patient exhibits an abrupt elevation of both SBP and DBP, a sudden deterioration of what was previously well-controlled hypertension, resistant hypertension, or clinical and biological indications suggestive of a particular form of secondary hypertension, then reversible causes should be suspected and investigated. The assessment and management of secondary hypertension are often more complicated in older patients. For example, although it is not uncommon to find evidence of atherosclerotic renal artery stenosis in older patients, it is often difficult to determine whether an identified atherosclerotic lesion in the renal artery is an incidental finding or is responsible for the elevation in BP.

Currently, the therapeutic strategy for a renovascular hypertension is to begin with a standard medical treatment as in essential hypertension and consider endoluminal or other interventions only after failure of the medical treatment.<sup>84</sup> Moreover, the indications for percutaneous or surgical interventions in case of renovascular hypertension should be judiciously considered because these interventions may be less efficacious and riskier in frail older individuals.<sup>85</sup> Sleep apnea is an often unrecognized but relatively common cause of high BP in older age. It should be considered in overweight individuals and those who complain of daytime somnolence or present snoring or irregular breathing during sleep.<sup>86</sup> Chronic renal insufficiency, obstructive nephropathy, and thyroid disease are other potential secondary causes of hypertension in older individuals. Assessment of serum creatinine alone may overestimate renal function in older patients. Alternatively, available formulas estimating the glomerular filtration rate should be used.<sup>87</sup>

Among other causes of secondary hypertension, medication-related BP elevation should always be investigated. Patients should specifically be questioned on use of nonsteroid anti-inflammatory drugs, nasal decongestants, corticosteroids, hormone replacement therapy, ephedrine-containing supplements, and other over-the-counter preparations, which many patients do not view as medication and fail to mention their use unless specifically asked.

Finally, resistant hypertension may also be because of nonadherence (eg, because of cognitive decline), and possible causes should be appropriately investigated.

Determining global CVD risk is currently advocated by guidelines in addition to the standard procedures of BP

assessment. Global risk assessment should take into account certain specificities for older adults, including

- Personal rather than family history is of importance. Indeed, with aging, heredity plays a less pronounced role, and it is more difficult for an older person to remember parents' medical problems.
- Auscultation and palpation investigating for a widened abdominal aortic pulsation and arterial bruits are useful for the diagnosis of abdominal aortic aneurysm with possible interventions providing a significant clinical benefit. Suspicion must be verified with ultrasound.
- BP change from supine to upright position should be systematically measured in older hypertensive subjects independently of symptoms such as dizziness, falls, or syncope.
- Assessment of arterial stiffness and intima-media thickness may be of help to better identify older but still robust hypertensive subjects at high risk of CVD complications. Evidence from large clinical trials in the very old, however, still remains weak.<sup>88</sup>

### Evaluating Frailty Level and Functional Status

As aforementioned, the term frailty is used to denote a multidimensional syndrome of reserve loss leading to a decline of physical, cognitive, psychological, and social functioning. Frailty is tightly related to, and even predictive of, the risk of dependence, hospitalization, institutionalization, and death.<sup>6,9,89,90</sup>

During the past 10 to 15 years, various clinical studies have produced a vast amount of evidence indicating that assessment of both frailty and functional status can provide valuable information in 3 fields,<sup>91–95</sup> namely

- Assess the risks of functional decline, morbidity, and mortality.
- Propose specific actions to prevent or to slow frailty.
- Define the risk/benefit balance of aggressive and chronic treatments and, therefore, adapt the therapeutic strategies in older adults. This approach avoids using age—or traditional specialty-specific scores—as sole criteria in the provision of health and social care services.

In the context of treatment of high BP levels, this last aspect is of major importance and will be further developed in the next chapters.

Aside from, and partly because of the lack of consensus in its definition, the detection of frailty encounters many challenges.

First, frailty is a multidimensional clinical entity, and its phenotypic presentation can be extremely heterogeneous in severity.

Second, frailty is a continuous phenomenon, and in reality, all older subjects present some degree of frailty and functional decline as compared to much younger individuals. It is, therefore, necessary to define the level of frailty, which can be considered as significant according to the objectives of the evaluation.

Third, assessment of frailty and functional status is time-consuming and often requires special skills. These factors, along with the fatalistic ageistic perception that not many things can be done to treat geriatric problems and to prevent their natural evolution, has led to the contention that the evaluation and management of frailty concerns only organized, multidisciplinary, specialized geriatric settings. This opens a

vast field of potential public health frailty screening strategies to be implemented.

The multitude of scales for measuring frailty and their heterogeneity reflect these different aspects. Certain scales are almost exclusively aimed to detect the physical consequences of frailty,<sup>7,93–95</sup> whereas others are much more multidomain<sup>91,92</sup>; some of these scales are very short and thus more adapted for rapid evaluation of frailty, whereas others are much more complete and obviously more time-consuming.

In the present review, we have chosen a visual and practical tool to determine functional profiling, which can guide treatment decisions. This visual score is based on the score established by the Canadian Study of Health and Ageing (CSHA).<sup>96</sup>

## Evidence for the Benefits of Antihypertensive Treatment in Older People

### Benefits on Cardiovascular Outcomes

HYVET showed in the setting of an RCT the beneficial effect of antihypertensive treatment versus placebo) on cardiac mortality and several other cardiovascular outcomes in octogenarians.<sup>97</sup> More recently, another RCT, the SPRINT (Systolic Blood Pressure Intervention Trial), showed benefits for a lower BP goal of SBP <120 mmHg in patients aged over 75 years,<sup>98</sup> albeit after excluding patients with loss of autonomy, cognitive disorders, diabetes mellitus, and history of stroke. Based mainly on the HYVET trial, the 2013 European Society of Hypertension/European Society of Cardiology Guidelines<sup>99</sup> for the management of arterial hypertension stated that in the elderly, there is evidence for benefits of antihypertensive treatment when treating individuals with initial SBP of >160 mmHg, whose SBP was reduced to values <150 mmHg. Guidelines also recommend that if pharmacological treatment for high BP results in lower SBP (eg, <140 mmHg) and treatment is not associated with adverse effects on health or quality of life, treatment does not need to be adjusted.

Interestingly, a post hoc analysis of both HYVET<sup>100</sup> and SPRINT<sup>98</sup> did not find a relationship between the benefits of antihypertensive treatment and patient frailty. Therefore, both studies concluded that antihypertensive treatment strategies and goals in frail older patients should be similar to treatment strategies used in the fittest subgroups of patients, with these results being ultimately incorporated in the 2017 Canadian guidelines.<sup>101,102</sup>

However, the very frail subjects were excluded from both the HYVET<sup>97</sup> and SPRINT trials<sup>98</sup> as was also the case in almost all previous clinical trials.<sup>12</sup> Moreover, these 2 trials were conducted in selected populations of relatively fit community-dwelling individuals and, furthermore, excluded those with clinically significant cognitive decline and dementia, multiple cardiovascular and other comorbidities, orthostatic hypotension, metabolic disorders, as well as patients with loss of autonomy.<sup>103</sup> The exclusion criteria in these 2 studies presented in Table 2 clearly indicate that the main findings cannot be automatically extrapolated to the totality of patients aged over 80 years. In addition, there is an open debate as to whether the method used for BP measurements in SPRINT potentially produces lower BP levels by 10 to 15 mmHg, which means that a BP level of 120 mmHg in

**Table 2.** Main Exclusion Criteria in HYVET and SPRINT Trials

Age, y	SBP	DBP	BP Regulation Physiopathology	Main Risks	Better BP Risk Marker	Management
65–80	↑↑	↑	High PR and AS	CV complications, cognitive decline	High SBP	Physical activities, assess TOD and global CVR, medical tt (SBP <140)
65–80	↑	↔↓	High AS	CV complications, cognitive decline	High SBP, PP, low DBP	Physical activities, assess TOD and Global CVR, medical tt (SBP <140)
>80	↑↑	↔↓	High AS	CV complications, falls	High PP, low DBP, OH	CGA, medical tt (SBP <150 or SBP <140 according functional status)
>80	↔	↓↔	High AS and comorbidities	CV complications, falls, loss of autonomy	Normal/low SBP, low DBP, normal/high PP, OH	CGA, deprescribing if SBP<130 or OH, fight polypharmacy

AS indicates arterial stiffness; BP, blood pressure; CGA, Comprehensive Geriatric Assessment; CV, cardiovascular; CVR, cardiovascular risk; DBP, diastolic blood pressure; HYVET, Hypertension in the Very Elderly Trial; OH, orthostatic hypertension; PP, pulse pressure; PR, peripheral resistance; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial; TOD, target organ damage; and tt, treatment.

SPRINT may correspond to a BP level of 130 to 135 mm Hg when using classical BP measurements.<sup>104,105</sup>

### Benefits on Cognitive Function

An important dimension of benefit of antihypertensive treatment would be the prevention of cognitive decline. Although epidemiological studies clearly indicate the relationship between higher BP and cognitive decline during long-term,<sup>53</sup> several methodological factors—such as short study duration, older participants—may explain the meager benefit for cognition in controlled studies (including HYVET) of BP lowering.<sup>59,60</sup>

These results seem to get some support, however, from a post hoc subgroup analysis of the recent Prevention of Dementia by Intensive Vascular Care trial; vascular care of 70- to 78-year-old individuals in a health care setting for 6 to 8 years affected neither primary nor secondary end points of cognitive function and autonomy.<sup>106</sup> The authors explain the overall negative results by the lack of contrast in cardiovascular risk reduction between the intervention and the control groups. They also suggest that the studied population was aged 70 to 78 years, whereas most observational data show an association between midlife hypertension and dementia.

Taken together, these results point out the importance of preventive and therapeutic actions to fight chronic high BP in younger ages. The BP goal to reach in order to obtain the best prevention of the cognitive decline and dementia remains unknown. Recently published results of the SPRINT MIND study (Systolic Blood Pressure Intervention Trial/Memory and Cognition in Decreased Hypertension)<sup>107</sup> among adults with hypertension older than 50 years (average age 68 years) demonstrated that intensive BP control (SBP<120 mm Hg) compared with standard BP control (SBP<140 mm Hg) did not significantly reduce the risk of developing dementia. However, because of early study termination and fewer-than-expected cases of dementia, the study might have been underpowered for this end point. The current evidence from observational and interventional studies does not support a clear benefit on cognitive function when starting antihypertensive treatment in older people and could even be deleterious in the very old frail people.

### Decision-Making Process in the Initiation and Follow-Up of Antihypertensive Treatment

Many patients may be reluctant to adhere to a given treatment, even when its benefits are clearly supported by clinical trials.<sup>108</sup> There are few studies on patient drug adherence in old age, although it seems obvious that both initial patient acceptance and long-term adherence are management issues that do not get simpler with increasing age. Beyond initial acceptance and implementation, antihypertensive treatment implies follow-up appointments, adjustments in drug schedules, and the burden of possible side effects. Patient adherence and even safety are better when these patients are involved in the decision-making process and are convinced of its benefits. Even when statistically significant, the benefits of a given treatment, in the patient's view, may be insufficient to warrant the effort. Physicians themselves may not always be convinced that the benefits of treatment are clinically relevant. Evidence from RCTs is typically based on observations in selected populations corresponding more or less to the actual patients treated by physicians. Again, it is also worth noting that control patients are often treated better than patients at large, the result of which is apt to lessen the differences between control and intervention groups. In a clinical study in older patients under antihypertensive treatment in Switzerland, only a small minority (4%–7%) clearly refused treatment.<sup>108</sup> Most patients wanted extensive medical information, although preferred delegating the final medical decisions to their physician.

Patients' preferences—and reluctance—must be understood and dealt with before taking a decision to treat or not to treat. Initial acceptance does not mean that patients understand and accept long-term therapy. A shared decision-making with regard to the treatment plan, which favors safety and adherence, requires detailed explanations not only at initiation but also repeatedly during follow-up. Shared decision-making is considered to be more complicated in the context of older age and multimorbidity. It is, however, highly relevant. Older patients with multimorbidity often face preference-sensitive decisions (ie, when ≥1 medically reasonable option is available and when there is no best strategy because the option depends on the patient's personal values and preferences) with regard to starting, continuing, and stopping medications.

## Guidelines for BP Goals and Therapeutic Strategies in Older Patients With High BP

### Blood Pressure Goals

The 2013 European guidelines based on the HYVET criteria recommend initiating an antihypertensive strategy in individuals  $\geq 80$  years with an SBP  $> 160$  mm Hg, and targeting SBP to  $< 150$  mm Hg.<sup>99</sup> The more recent North American Guidelines propose not to modify therapeutic targets based on age and frailty level.<sup>101,102</sup> It is, however, very difficult to find common BP goals in the different National and International guidelines:

The Canadian 2017 guidelines propose to target an SBP of  $< 120$  mm Hg for all individuals aged over 75 years.<sup>101</sup> The 2017 American College of Cardiology/American Heart Association guidelines indicate that a BP  $< 130/80$  mm Hg should be targeted after the age of 65 years.<sup>102</sup> The 2018 guidelines propose a BP goal of  $< 140/90$  mm Hg for individuals older than 65 years.<sup>109</sup> Finally, the 2017 American College of Physicians/American Association of Family Physicians guidelines propose to target a BP  $< 150/90$  mm Hg.<sup>110</sup>

One can also observe important discrepancies in the definition of elderly or older adults. In the clinical studies during the 80s on the Hypertension in the elderly subjects over 60 or 65 years old were included, whereas presently this definition is mainly used for subjects  $> 75$  or  $> 80$  years old. This diversity is also found in the above-mentioned guidelines with variable age thresholds between 65 and 80 years old. We recognize that although these discrepancies are highly confusing, they reflect the dramatic demographic, cultural, and biomedical changes of the last few decades and the vast heterogeneity in functionality among older subjects. For this reason, we think that functionality/frailty/autonomy criteria for the potential adaptation of therapeutic strategies. We use often the age threshold of 80 years to define older individuals because, currently, the percentage of people with severe loss of functionality and loss of autonomy dramatically increases after that age. For this reason, the specific diagnostic and therapeutic strategies discussed in this article mainly apply to individuals aged  $\geq 80$  years.

### Therapeutic Strategies

With regard to nonpharmacological interventions for lowering BP, although benefits have been shown in younger populations, there is little evidence from controlled studies in hypertensive patients aged 80 plus. Some of the proposed lifestyle changes,<sup>111</sup> including weight reduction, Dietary Approaches to Stop Hypertension/Mediterranean diet, dietary sodium reduction, physical activity, and moderate alcohol consumption may, however, not be appropriate or relevant and may even be detrimental. Thus, a weight reduction in patients  $> 80$  years easily induces a loss of muscle mass (sarcopenia) and can even cause cachexia, unless an intensive physical training program and adequate protein supplementation are concomitantly applied.<sup>112</sup>

Equally, an excessive salt reduction might induce hyponatremia, malnutrition, and orthostatic hypotension with increased risk of falls. Physical activity adapted to the functional capacities of the older person and to his or her preferences is of major importance, even if not meeting the amount

recommended by current guidelines, which is similar for older and younger adult subjects.<sup>113</sup> Finally, excessive alcohol intake should be discouraged, not only because of its pressor effect but also mainly because of increased risk of falls and confusion.

In older individuals, in which polypharmacy (including antihypertensive agents) is a frequent phenomenon, drug-related problems are directly correlated with the number of drugs and, therefore, starting with monotherapy should be the rule.

Most international guidelines propose the same 5 antihypertensive drug classes as for younger subjects: thiazide diuretics, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blockers (ARB), and beta blockers (BB). The American guideline on antihypertensive treatment in patients  $> 60$  years lists the adverse effects of drug classes but does not specifically advocate a particular drug class.<sup>110</sup> The British NICE guidelines (National Institute for Health Care Excellence) do not include BB as a first line treatment in older adults.<sup>114</sup> The European guidelines mostly favor a calcium channel blocker or a thiazide diuretic in the absence of a compelling disease-specific indication, in addition to lifestyle change recommendations when the latter is insufficient to achieve BP control.<sup>99</sup> We have furthermore recently proposed that in patients  $> 80$  years, ACE inhibitors should be among the first line medications because these represented 1 of the 2 drug classes used in HYVET.<sup>115</sup> However, the findings of some clinical studies argue against the use of ACE inhibitor as the first choice in older adults<sup>116</sup> and propose replacing them by ARBs.<sup>117</sup>

It is important to regularly check for all potential clinical and biological side effects and the impact of these treatments on the functional status and quality of life of the older patients. Table 3 shows the most frequent adverse effects of these drugs and the precautions to be considered in older adults. However, we should always bear in mind that in this population, medication-induced side effects are more frequent, more severe, and less specific than in younger adults.<sup>118</sup> Hence, all antihypertensive drugs can be responsible for certain common clinical manifestations and conditions such as fatigue, confusion/delirium, orthostatic hypotension, and falls.

A combination antihypertensive therapy to control BP should be considered in the course of treatment only if the indication seems relevant after a judicious benefit/risk assessment. According to authors' experience, a third drug can be added if necessary, after a new medication review to avoid drug-related side effects. Moreover, great care must be taken if  $> 3$  antihypertensive drugs are combined in individuals aged over 80 years.

### Should Frailty Status Influence Antihypertensive Treatment in Older Adults?

Several studies have demonstrated that stratification of older patients based on the level of frailty and functional status could greatly improve and predict short and long-term complications of therapeutic strategies when treating cardiovascular and metabolic diseases, such as diabetes mellitus,<sup>119</sup> chronic heart failure,<sup>120</sup> transcatheter aortic valve replacement,<sup>121</sup> cardiac surgery,<sup>122</sup> and atrial fibrillation.<sup>123</sup> In this respect, it is



**Table 3. Antihypertensive Drugs: Adverse Effects and Precautions in Individuals Aged 80+ Years**

Drug Class	Most Common Adverse Effects	Special Precautions/Considerations in Old Individuals
CCB Dihydropyridine CCB Non dihydropyridine CCB	Signs related to sympathetic activation (flushing, headache, tachycardia) are less frequent than in younger subjects. Lower limb edema (frequent since many other factors for LLE). Bradycardia, AV block, worsening heart failure, constipation (verapamil), fatigue, dyspnea.	LLE, which is relatively frequent with these drugs, can be erroneously interpreted as a clinical sign of heart failure. In addition, LLE can contribute to the decrease in social and physical activities for practical reasons (difficulties in walking with shoes). Second-line selection; diltiazem can also cause LLE. With verapamil, LLE is unusual, but constipation may be a major problem in very old individuals, as it can lead to fecal impaction, with nausea, anorexia, delirium, and functional decline. Never combine verapamil with $\beta$ -blockers.
Diuretics Thiazide Loop diuretic	Hyponatremia, hypokalemia, hyperuricemia and gout attacks, hypotension, dehydration. Similar to Thiazides	For both thiazide and loop diuretics: Diuretic should be titrated according to the patient's volemic status. The latter may be difficult to assess in very old and frail individuals. Creatinine and electrolyte monitoring is warranted after each dose change. Association with SSRI antidepressants increases the risk of severe hyponatremia. Risk of aggravation of urine incontinence. For this reason, diuretics may have an impact on the social life of the patient and can contribute to his/her isolation. Other patients often do not take their treatment if they want to have outdoor activities. Thiazide-like indapamide has been tested in the only RCT specific for subjects >80 y. Small doses (up to 25 mg of HCTZ or equivalent) are safe and well tolerated. Loop diuretics are not indicated for hypertension unless there is severe renal insufficiency (estimated creatinine clearance <30 mL/[min $\cdot$ 1.73 m $^2$ ]). In the presence of both hypertension and heart failure, loop diuretics can be used for both diseases, either alone or in combination with thiazides.
ACE inhibitors	Dry cough, hyperkalemia, rash, angioedema, dizziness, fatigue, acute renal failure	ACE inhibitors have been tested in the only RCT specific for subjects >80 y. Avoid if you suspect dehydration, do not simultaneously increase diuretics to avoid a worsening in renal function. Regular control of creatinine and potassium levels.
Angiotensin II receptor antagonists	Hyperkalemia, rash, dizziness, fatigue, acute renal failure	The same as for ACE inhibitors: Do not combine ARB with ACE inhibitor or renin inhibitor. Be cautious with aldosterone antagonist because of increased risk of hyperkalemia.
$\beta$ -adrenoreceptor antagonists ( $\beta$ -blockers)	Bradycardia, cardiac decompensation, peripheral vasoconstriction, bronchospasm, fatigue, depression, dizziness, confusion, hypoglycemia	Fatigue, which is multifactorial in older subjects, can be accentuated. Nightmares, sleep disturbances, depression, and confusion may be present especially for the $\beta$ -blockers crossing the blood brain barrier. Cardiac conduction problems can also be aggravated. Caution when used in combination with acetylcholinesterase inhibitors (for Alzheimer disease): risk of major bradycardia.
Aldosterone antagonists	Hyperkalemia, hyponatremia, and gastrointestinal disturbances, including cramps and diarrhea, gynecomastia	Aldosterone antagonist should not be given in instances of severe renal insufficiency, estimated creatinine clearance <30 mL/(min $\cdot$ 1.73 m $^2$ ) or hyperkalemia. Creatinine and electrolyte monitoring is warranted after each dose change.
$\alpha$ -adrenoreceptor antagonists ( $\alpha$ -blockers)	Dizziness, fatigue, nausea, urinary incontinence, orthostatic hypotension, syncope	Usually not indicated. Risk of hypotension (orthostatic, postprandial) and syncope.
Central $\alpha$ -adrenoreceptor agonists	Drowsiness, dry mouth, dizziness, constipation, depression, anxiety, fatigue, urinary retention or incontinence, orthostatic hypotension, confusion, and delirium	High risk of delirium and confusion. Depression, which is atypical and frequent in older subjects (and tricky to diagnose vs cognitive disorders), can be aggravated.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blockers; AV, atrioventricular; CCB, calcium channel blockers; LLE, lower limb edema; HCTZ, hydrochlorothiazide; RCT, randomized controlled trial; and SSRI, selective serotonin reuptake inhibitors.

equally important to take into account the frailty and functional status when treating hypertensive patients.

The objective is to make the optimal choice of diagnostic and therapeutic strategies to avoid an a priori exclusion because of advanced age and aggressive therapies targeting

only life prolongation. This task is achieved by assessing the degree of frailty to define the benefit/risk ratio of diagnostic and therapeutic strategies of older patients with CVD. At present and in the future, cardiologists are faced with managing an increasing number of older patients, with the mean age of

patients hospitalized in cardiology departments currently often >80 years.<sup>124</sup> The main consequence of these demographic changes is the presence of multiple comorbidities, geriatric syndromes, frailty, and loss of autonomy—all of which complicate the evolution and treatment of chronic CVD.

Among older adults with heart failure, management is further hindered by other common geriatric impairments, including incontinence, falls, and frailty.<sup>125</sup> In addition, the vast majority of hospitalized patients in geriatric departments present multiple chronic CVD risk factors and disease, such as hypertension, diabetes mellitus, atrial fibrillation, heart failure, valvular disease, ischemic heart disease, etc.<sup>126</sup> Consequently, geriatric cardiology (or cardio-geriatric medicine) has been—and needs to be further—developed to combine several decisional factors: age-attuned evidence-based management of CVD, comprehensive geriatric assessment (CGA), medication optimization, team-based coordination of care, and involvement of the patient and his/her caregivers in decision-making.<sup>127</sup>

Therefore, the best answer to the key question “should frailty level influence therapeutic strategies when treating hypertensive older people?” is to define the threshold of frailty and functional decline beyond which treatment should be adapted. In our expert review published in 2016, we defined this threshold as “people living in nursing homes or needing assistance on a daily basis for their basic activities” which as mentioned may represent up to 35% of those aged over 80 years.<sup>115</sup> These are in fact the individuals who

- Showed negative relationships between BP levels and morbidity-mortality, especially when receiving antihypertensive medications.
- Have always been excluded from clinical trials which have established the benefits of antihypertensive treatment.

Adequately defining the proper threshold helps to assess whether the expected benefits of treatment outweigh the risks in such a population with decreased life expectancy and decreased tolerance to stress.<sup>128</sup> The CGA method, that is, a multidisciplinary diagnostic and treatment process in addition to assessment of multimorbidity,<sup>129,130</sup> identifies medical, psychosocial, and functional limitations of an older person to develop a coordinated plan to maximize overall health with aging.<sup>131,132</sup>

However, in most cases, CGA is too complex and highly time-consuming for nongeriatricians. Thus, an effort should be made to propose valid algorithms for the classification of older patients according to their functional status, which is both fast and can be performed by most health professionals. Figure 1 is an example of classification according to the frailty status based on the CSHA score.<sup>96,133</sup> This visual numeric scale represents a practical decision-making tool to adapt antihypertensive strategies. We propose this approach to discriminate between 3 profiles of patients, that is, those with preserved functional status (preserved function, groups 1–3 of the CSHA score), those with loss of function but preserved autonomy for the ADL (loss of function/preserved ADL, groups 4–5 of the CSHA score), and those with severe loss of functional impairment and loss of autonomy for the ADL (loss of function and altered ADL, groups 6–9 of the CSHA score).

The therapeutic strategies for BP lowering in each of these 3 groups are further expanded in the following section and schematically depicted in Figure 2.

## Adaptation of the Treatment in 3 Different Functionality/Autonomy Groups

### Older Adults With Preserved Functional Status (Preserved Function Profile)

This profile includes functionally independent older subjects without medically relevant comorbidity or those with satisfactorily-controlled disease symptoms and without significant impact on functional status. In these patients, we should consider full therapy to achieve outcomes similar to that of younger patients.

### Older Adults With Moderate Functional Decline and Preserved Autonomy For ADL (Loss Of Function/Preserved ADL Profile)

Older subjects with this profile have moderate functional decline and a dependence in instrumental ADL (IADL) in the absence of dependence in ADL. Patients of these groups commonly have 1 or 2 comorbidities, as well as moderate cognitive and functional decline (consider adapted/tailored therapy including deprescribing).

We estimate that an important percentage of these patients (probably 25% to 40% for group 4 and the large majority of group 5) were excluded from the HYVET, hence the reason we consider subjects in these groups as being in a gray zone regarding evidence of treatment benefit.

To detect the presence and extent of frailty and impaired functional capacity in this profile, CGA should be performed. Indeed, CGA ultimately allows the identification of comorbidities, geriatric syndromes, and the degree of functional impairment and loss of autonomy for the different ADL, thus allowing the possibility to consider tailored therapy: patients with few comorbidities and minor loss of autonomy will have antihypertensive therapeutic strategies similar to the preserved function profile, whereas those with multiple comorbidities, presence of geriatric syndromes, and dependence in ADL will have an approach similar to the loss of function and altered ADL profile described below.

### Older Adults With Significant Loss of Function and Loss of Autonomy for ADL and Limited Life Expectancy (Loss of Function and Altered ADL)

This profile is identified by the presence of at least one of the following: multiple comorbidities, severe dementia, several geriatric syndromes, or dependence in ADL. Most patients in this group are aged  $\geq 85$  years.

Treatment in patients having this profile should be reassessed, in addition to considering the possible use of a life expectancy calculator.<sup>134</sup> Preserving symptom relief and quality of life is the primary goal of care. Drug prescription should very often be reevaluated for hierarchization of priorities and optimization. Because iatrogenic risk is very high, specialists should work closely with general practitioners (GPs), pharmacists, and caregivers.

Thus, while keeping SBP <150 mmHg as the evidence-based target, antihypertensive drugs should be reduced



**Figure 1. Profiles according to frailty and functional status in patients 80 years and over.**<sup>96,133</sup> This visual numeric scale based on the Canadian Study of Health and Ageing (CSHA) score represents a practical tool for the initial profiling of 80+ patients to help decide whether to adapt antihypertensive strategies. Subjects with a preserved function profile (groups 1–3 in the CSHA classification) feature a preserved functional status, are active and independent, possibly present chronic diseases, are well-controlled and their somatic and cognitive functionality remains satisfactory. On the other end of the spectrum, subjects with a loss of function and altered activities of daily living (ADL) profile (groups 6 to 9) require daily assistance for basic activities of daily living. In between, we identify subjects with a loss of function/preserved ADL' profile (groups 4 and 5); these subjects are generally slowed down, have certain dependencies in instrumental ADL (IADL), although are generally autonomous for ADL. They may commonly have well-controlled comorbidities and moderate cognitive and functional decline. This profile requires a more detailed assessment of their functional status using the different scales for comprehensive geriatric assessment.

or even stopped for safety reasons if SBP is lowered to SBP <130 mmHg, or in cases of orthostatic hypotension, thus maintaining the 150 to 130 mmHg on-treatment SBP values as a safety range.<sup>115</sup> Other factors that may potentially be decreasing BP and inducing orthostatic hypotension, including malnutrition, dehydration, and other medications, should be identified and corrected.

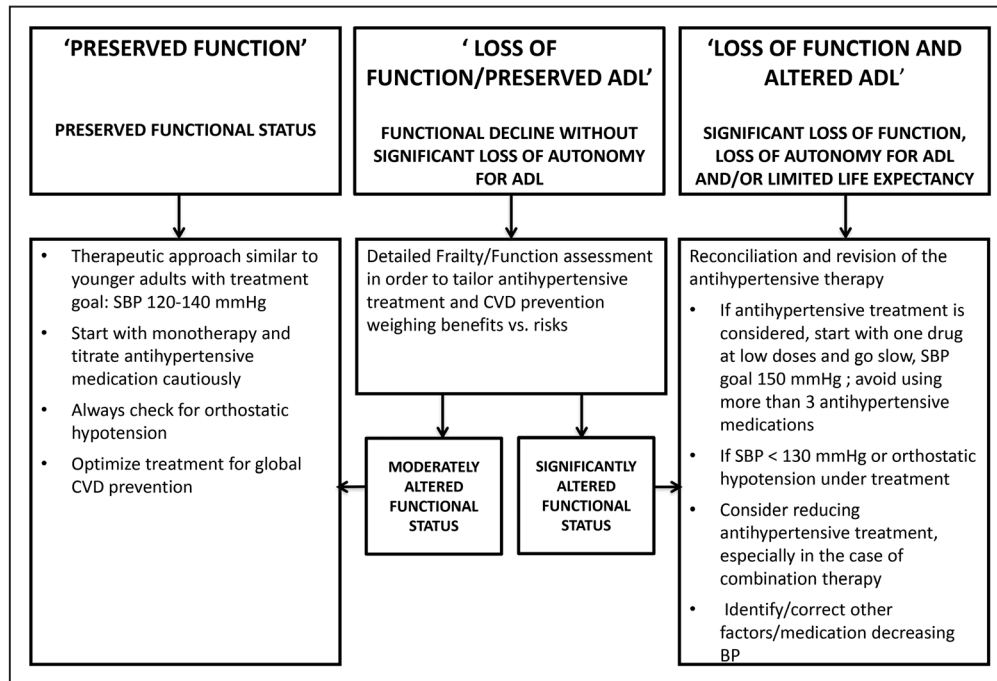
A particular effort should be made in educating physicians on also deprescribing antihypertensive drugs when necessary. There is also prospective, observational evidence that, among older individuals, deprescribing can save costs and be performed successfully without harm to the patient.<sup>135,136</sup> However, limitations of the existing evidence include, among others, (1) only few of the studies have investigated clinical outcomes; (2) most of the trials had small sample sizes; (3) an insufficient duration of follow-up; and (4) insufficient power to detect clinically significant differences in outcomes. Specifically, there are no RCTs with antihypertensive drugs in this profile of patients. Such studies are desperately needed, given that physicians—especially GPs—are very skeptical

and wary of reducing therapy in the CVD field. Again this situation points to the necessity for a close collaboration between GPs, geriatricians, cardiologists, pharmacists, and nurses to modify prescribing/deprescribing practices. Naturally, close supervision of the patient after deprescribing is required.

Finally, we have previously pointed out the pressing necessity of solid scientific evidence based on registries, observational studies, large longitudinal cohorts, and mainly controlled trials in subjects with severe frailty.

### Conclusions and Perspectives

There is an open debate on whether the management of arterial hypertension, and more specifically the treatment goals of antihypertensive therapy, should be modified in octogenarians according to their functional reserve and frailty levels. Chronological age should not be the main criterion for adapting therapeutic strategies, because of the large heterogeneity in the pace and consequences of the aging process among older adults. For this reason, geriatricians propose the assessment of functional status and frailty through the CGA as a tool



**Figure 2. Decisional algorithm for the management of hypertension in subjects aged 80+ years.** This algorithm proposes adapted therapeutic strategies according to the classification proposed above (Figure 1). In the preserved function profile, antihypertensive strategies should be those proposed for younger subjects (between 65 and 75 y). For the loss of function and altered activities of daily living (ADL) profile, the antihypertensive therapeutic strategy should be different comparatively to robust patients. The decision for antihypertensive treatment in patients with a loss of function/preserved ADL profile should be individualized according to the results of the comprehensive geriatric assessment. CVD indicates cardiovascular diseases; and SBP, systolic blood pressure.

to tailor the management of hypertension and other chronic diseases in older people.

Despite significant advances, CGA remains time-consuming, complex, and difficult to apply in general clinical practice. This leads to indistinctness among health professionals regarding the understanding of who is frail and to what extent frailty should be taken into account when treating hypertension. This indistinctness has been facilitated by the lack of clinical trials in the more complex older patients with cognitive and functional decline, multimorbidity, frailty, and disability.

- In this review, we propose a pragmatic approach by classifying older patients in 3 functional profiles based on simple clinical criteria.
- For individuals with preserved autonomy and preserved functionality (preserved function profile), strategies should be those proposed by the various national and international guidelines for the younger old adults (65–75 years).
- For individuals with significant cognitive and functional decline, loss of autonomy, overt frailty, and limited life expectancy (loss of function and altered ADL profile), therapeutic strategies should be meticulously reassessed and in which deprescribing is also considered as appropriate.
- For individuals between these 2 groups, that is, those with moderate functional decline and frailty, but with preserved autonomy for ADL (loss of function/preserved ADL) profile, a more detailed geriatric assessment is needed to define the benefit/risk balance of the different therapeutic strategies.

These statements are predominantly based on observational data and on clinical experience, and, therefore, there is an imperative need for well-designed controlled clinical trials focused on the most frail older people to generate strong evidence relative to therapeutic strategies in this specific population group.

## Disclosures

A. Benetos has been invited as a speaker in symposia organized by Novartis, Servier, Menarini, and Bayer over the past 5 years. T. Strandberg has had educational, consultative and research cooperation with several companies (including Novartis, Orion, Servier) and other entities interested in hypertension and its treatment. The other author reports no conflicts.

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