REVIEW

Arterial hypertension after age 65: from epidemiology and pathophysiology to therapy. Do we know where we stand?

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Abstract

Arterial hypertension is a prevalent disease with great harming potential. After the age of 55 years the remaining lifetime risk of hypertension amounts to 90%. Despite the constant advances some important issues such as the cut-off blood pressure for the initiation of antihypertensive therapy or the therapeutic goal are debated.

In this review, we present — based on the available literature — the current concepts concerning the pathophysiology, epidemiology and antihypertensive therapy in patients aged 65 years or older.

The pathophysiology of hypertension in older patients in principle rests on stiffening of large conduit arteries, which leads to greater systolic and lower diastolic blood pressure. This in most older patients results in isolated systolic hypertension. Additionally most of these patients have low-renin hypertension. Data from large-scale clinical trials indicate that therapy of such individuals with thiazide-like diuretics and long-acting dihydropiridine calcium channel blockers as first-line medications reduces risk of complications. Based on results of recently published trials, meta-analyses, and prospective observations, the optimal on-treatment blood pressure values for most older hypertensive patients should be set within the 130–139 mmHg range. At present, lower values of standard office blood pressure in this group of patients have not been shown to be associated with additional benefits, and may be associated with a greater risk of adverse events.

In conclusion, we recommend that for most patients aged 65 years or more, standard office systolic blood pressure should be cautiously reduced to within 140 and 130 mmHg, preferably with a thiazide-like diuretic, long acting dihydropiridine calcium channel blocker or their combination.

Key words: older patients, hypertension, isolated systolic hypertension, antihypertensive therapy

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INTRODUCTION

Upon reaching the age of 55–60 years, the remaining lifetime risk of becoming hypertensive amounts to 90% [1, 2]. Arterial hypertension is considered to be one of the leading causes of mortality of older adults, mostly by increasing the risk of such cardiovascular (CV) complications as myocardial infarction, stroke, heart failure or dissection of aortic aneurysms [3–10].

Primary hypertension in older adults is associated with different pathophysiologic background than primary hypertension seen in younger adults. This in large part is related to the ageing process of the CV system and kidneys. The repetitive

haemodynamic force exerted during each heart cycle by the contraction of the left ventricle leads to thickening and stiffening of the myocardium, due to accumulation of lipofuscine [11]. The repetitive distensions and recoils of the aorta, which securing the non-zero, appropriate level of diastolic blood pressure (DBP), lead to remodelling of the aorta [12]. In this process, elastine fibres are becoming fragmented, and the amount of collagen increases, along with a change of the prevailing type of collagen [13]. Likewise the cellular component of the aortic media changes, with increase in fibrocytes [14], that results in progressive thickening and stiffening of the

aorta [12–14]. This alteration has three effects of paramount importance to the pathophysiology of arterial hypertension in older patients.

First, the reduced compliance leads to less buffering of systolic pressure, which in turn causes higher values of systolic blood pressure (SBP).

Second, this means that less energy is stored and subsequently given back during diastolic elastic recoil of the aorta to the blood, resulting in lower DBP.

Third, the pressure pulse wave travels faster in stiffer aortic wall, which results in faster return of reflected wave which additionally augments systolic and lowers diastolic pressure [15, 16].

Another important issue in relation to ageing is gradual loss of renal function. Apart from steady decrease of glomerular filtration rate, at a rate of approximately 1% per year after the age of 35 years, the ageing kidney loses its ability to maintain adequate baseline renin production. The baseline plasma renin activity (PRA) may thus be decreased by 30% to 50%. In addition, the secretion of renin in response to typical stimuli such as assumption of supine position, low sodium diet or volume depletion (as in bleeding) is also blunted [17, 18]. Earlier research by Laragh et al. [19, 20] and some more recent studies and trials [21, 22] suggested that antihypertensive therapy in the older patients might be guided by PRA [23, 24]. The fact that in the older patients hypertension is associated with low PRA may have important therapeutic consequences, in that the long-acting calcium channel blockers (CCB) and diuretics may be more efficacious than medications acting via blockade of the renin–angiotensin–aldosterone system.

BLOOD PRESSURE LEVEL AND CARDIOVASCULAR RISK IN OLDER PATIENTS

The concept of harm associated with increasing level of blood pressure in older subjects was evolving over the past 90 years. Whereas still in the 1930s it was believed that higher values of especially SBP in older people were essential for the preservation of good health [2, 25] (hence the term 'essential hypertension' currently usually replaced by that of primary hypertension). Early results from the Framingham Heart Study indicated that in older subjects SBP rather than DBP conferred the bulk of the risk associated with hypertension [26]. This finding was independently confirmed by the MRFIT study [27, 28]. On the other hand, a number of clinical trials performed in the 1980s concentrated on DBP alone, to the point that some of them did not even report systolic pressure values. The culmination of this concept was the seminal meta-analysis in 1990 which established the relation between level of diastolic pressure and CV risk, supported by observations that upon lowering of diastolic pressure, CV risk is decreased [29, 30]. However, it was not until 10 years later that a similar meta-analysis, performed on data of individual patients at or above the age of 60 years with systolic pressure

exceeding 159 mmHg, demonstrated that greater systolic pressure is associated with increasing risk of CV complications, per each 10 mmHg greater SBP there was 20%–30% higher risk of CV events as well as CV and all-cause mortality [6]. After adjustment for systolic pressure, lower diastolic pressure was associated with greater risk of death, underlying the importance of pulse pressure as an independent risk factor in older patients with isolated systolic hypertension. These results were in line with earlier research which demonstrated that indices of arterial stiffening, primarily pulse pressure and pulse wave velocity, are incrementally associated with elevated risk of CV events in patients with a broad spectrum of clinical settings [31], including older patients with isolated systolic hypertension, end stage kidney disease, and diabetes mellitus [31–36].

THE EVIDENCE TO SUPPORT THERAPY

Over the past quarter of century, four major placebo-controlled trials of antihypertensive therapy in older patients with isolated systolic hypertension have been published. The Systolic Hypertension in the Elderly Program (SHEP), published in 1991, included 4736 patients aged 60 years or more (57% women) who were randomly assigned either to active regimen based on thiazide-like diuretic chlorthalidone with possible addition of atenolol, and reserpine, or matching placebos. After the average follow-up of 4.5 years actively treated patients as compared to the placebo group had 36% lower risk of all stroke, 27% reduction of the risk of coronary artery disease, and 32% reduction of the risk of combined CV events (all p < 0.01) [37, 38]. The results of this trial have to be analysed cautiously as only 1% of the original screening population was finally enrolled. In the Systolic Hypertension in Europe (Syst-Eur) trial, 4695 patients aged 60 years or more (66% women) were randomised to receive either nitrendipine (a dihydropiridine calcium channel blocker [CCB-DHP]) based therapy with possible sequential addition of enalapril, and hydrochlorothiazide, or matching placebos. After a median follow-up of two years the trial was stopped prematurely because actively treated patients had 42% lower risk of all stroke, 26% reduction of the risk of cardiac events, and 31% reduction of the risk of CV events combined (all p ≤ 0.03) [39]. The Systolic Hypertension in China (Syst-China) trial replicated the results of Syst-Eur in the Chinese population, showing, after two years of follow-up on average, 38% reduction of all stroke, 39% reduction of CV mortality, and 39% reduction of the risk of all-cause death (all p ≤ 0.03) [40]. The results of Syst-China were at times disregarded due to the fact that instead of randomisation the protocol provided for alternate allocation of patients into the respective arms. However, as can be judged by the comparison of baseline characteristics between the two groups, such study design did not result in a systematic bias [40, 41]. Finally, the Hypertension in the Very Elderly Trial (HYVET) included 3845 patients (61% women) at or above the age of 80 years and randomly assigned to active

treatment based on thiazide-like diuretic indapamide with possible addition of perindopril or matching placebos [42]. After follow-up of 2.1 years the actively treated patients had 30% lower risk of stroke (p = 0.06), 23% lower risk of CV death (p = 0.06), and 21% lower risk of death of all causes (p = 0.02). Moreover, the actively treated patients had 64% lower risk of heart failure (p < 0.001) [42]. However, this benefit may be attributed to a confounding factor, namely the medications used to treat hypertension in this trial came from drug classes constituting the cornerstone of medical therapy of heart failure. The interpretation of the HYVET trial is challenging because the population enrolled was extremely healthy and only about one third of the patients in this group of very old hypertensives had isolated systolic hypertension. Both facts preclude the application of the study results to the overall population of hypertensives above the age of 80 years [43, 44].

A number of active control studies were performed in a population of older patients with hypertension. Of these, the Losartan Intervention For Endpoint reduction in hypertension (LIFE-ISH, substudy in patients with isolated systolic hypertension and left ventricular hypertrophy) trial showed that therapy based on losartan with possible addition of hydrochlorothiazide, as compared to therapy based on atenolol with possible addition of hydrochlorothiazide, reduced the composite endpoint of stroke, myocardial infarction and CV death by 25% (p = 0.06) [45]. Of particular importance is the fact that the trial did not demonstrate blood pressure difference between the two therapeutic arms [45]. The Second Australian National Blood Pressure Program (ANBP2) demonstrated 11% (p = 0.05) reduction of the relative risk of all CV events or death from any cause with therapy based on enalapril as compared to diuretic-based regimen. However, this marginal effect was driven by the outcome in men enrolled to the study population. No effect was seen in women [46]. Like in the LIFE-ISH trial [45], the ANBP2 did not show the between-group difference in blood pressure [46]. The SCOPE (The Study on Cognition and Prognosis in the Elderly; candesartan/hydrochlotothiazide + amiloride vs. placebos) [47], SHELL (The Systolic Hypertension in the Elderly study; lacidipine vs. chlorthalidone) [48], and INSIGHT-ISH (The International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment, subanalysis in isolated systolic hypertension; nifedipine GITS/atenolol/enalapril vs. hydrochlorothiazide/atenonol/enalapril) [49] did not produce evidence in favour of the use of any particular medications. Overall, current evidence supports use of diuretics and long-acting CCB-DHP as the mainstay of antihypertensive therapy in older patients with isolated systolic hypertension and no other compelling indications [50–54].

Of the diuretics the preferred group would include thiazide-like compounds, as hydrochlorothiazide has been shown to be of dubious value at lower doses and potentially fraught with unfavourable side effects at blood pressure lowering doses equipotent to those of indapamide or chlorthalidone [55]. Furthermore, hydrochlorothiazide, which is a photosensitiser, has been shown to increase the risk of nonmelanoma skin cancer. In a nationwide Danish study the cumulative dose of hydrochlorothiazide of more than 50,000 mg has been associated with 29% greater risk of basal cell carcinoma (p for trend < 0.001) and 398% greater risk of squamous cell carcinoma (p for trend < 0.001) [56].

Based on the results of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), where regimen based on combination of long-acting CCB-DHP amlodipine and angiotensin-converting enzyme inhibitor (ACEI) perindopril and was superior to combination of β-blocker atenolol and thiazide diuretic bendroflumethiazide [57], the use of the combination of ACEI and CCB-DHP has been advocated, including the older patients [57, 58]. Indeed the ASCOT results indicated that the benefit was present independent of whether the patients were younger than 60 years or older [57]. However, the use of atenolol as a comparator has been widely criticised [59–61], as the medication is believed to confer little or no benefit in hypertensive subjects [62, 63]. Moreover, in older subjects atenolol may even increase central blood pressure, as was demonstrated in the CAFE study [64].

Another issue is the use of alpha-adrenolytic medications such as doxazosin, which may be tempting especially in older male patients with hypertension and coexisting benign prostatic hyperplasia. Since the publication of an initial report of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [65, 66], doxazosin has been moved to the third or even fourth line of antihypertensive regimens, especially in the elderly [54]. However, the closer scrutiny of the ALLHAT report reveals possibility of significant bias [65]. First, during the run-in period of the trial patients were to undergo a wash-out period, during which previous antihypertensive therapy was discontinued. Then, the patients were randomly assigned to one of four arms, including chlorthalidone and doxazosin. The doxazosin arm was discontinued prematurely because significantly more patients had episodes of heart failure and CV disease. However, neither the primary outcome of coronary heart disease, nor all-cause mortality differed between the doxazosine and chlorthalidone groups [65]. Of note, patients in the doxazosin arm during the entire trial had systolic pressure higher by 2 to 3 mmHg than individuals assigned to chlorthalidone; the difference was likely to account for a 5% to 9% difference in outcome [6]. Clearly, doxazosin is neither first nor second line antihypertensive medication in the older patients, especially in monotherapy of patients with or at high risk of developing heart failure. Doxazosin must be used with caution and should best be avoided in patients with orthostatic hypotension. However, in patients in whom escalation of antihypertensive regimen is needed, especially those who would not tolerate

anti-aldosterone compounds, or in male subjects with co-existing benign prostatic hyperplasia, doxazosin may still be useful, although to limit the risk of side effects the long-acting formulation should be preferred [54].

An all-important question of the cut-off for the definition of hypertension and the initiation of antihypertensive therapy has recently been refueled with the publication of the results of the SPRINT trial results and SPRINT-AGED subanalysis [67]. SPRINT was a randomised trial evaluating the intensive (< 120 mmHg) or standard (135–139 mmHg) goal of antihypertensive therapy. The study, which was carried according to the PROBE (prospective, randomised, open-label, blinded endpoint assessment) design [68], included hypertensive patients aged over 50 years with SBP values of between 130 and 180 mmHg. The patients had to be free from diabetes mellitus but otherwise they had to be burdened by high CV risk profile [67]. The main report described the data on the initial cohort of 9361 patients. Overall, the trial demonstrated significant reduction of relative risk of sustaining the primary composite endpoint of non-fatal acute coronary syndrome (including non-fatal myocardial infarction), non-fatal stroke, non-fatal exacerbation of heart failure and CV death, by 25% (p < 0.001) and all-cause death by 27% (p = 0.003) [67]. The subgroup analysis in older patients showed that the relative risk of composite primary endpoint as described above, was reduced by 34% (p = 0.001) and death of all causes by 33% (p = 0.009) [69]. In the entire study group, these benefits were achieved at the statistically significant cost of an increase in the risk of hypotension, acute renal failure, and hyponatraemia of the magnitude similar to that of the reported benefit [67, 70]. In the subgroup of patients older than 75 years, there was a marginally non-significant trend for a greater relative risk of hypotension by 71% and syncope by 23% [69].

The interpretation of both reports of the SPRINT trial poses several problems. First, the blood pressures reported by the authors were not standard office measurements. Instead, blood pressures were measured with an automated oscyllometric device with the patient left at his or her leisure without presence of a healthcare professional. A number of studies demonstrated that the unattended blood pressure measurements may be associated with 9.0–15/6.0–8.0 mmHg lower SBP/DBP values as compared to standard office measurements [71–73]. This led Filipovský et al. [73] to the conclusion that the level of unattended blood pressure corresponding to office blood pressure of 140/90 mmHg should be 125/82 mmHg, systolic and diastolic pressure, respectively.

All of the recently performed large-scale clinical trials used measurement of blood pressure in an attended fashion. This drawback makes the comparisons of the outcome of these trials and the SPRINT feasible only when the adjustment for the difference in blood pressure using different methods is taken into consideration [74]. However, this is not where the interpretational problems of the SPRINT trial stop. In order to

separate the groups on the basis of achieved blood pressure, the provision had been made in the protocol to the effect that a patient randomised to standard therapy with the average SBP of 130 mmHg or less during a single visit or with the average SBP of 135 mmHg or less during two consecutive visits should have his or her medications tapered down in order to maintain the SBP between 135 and 139 mmHg [67, 75]. According to data presented in the main report of the trial, at the initial visit alone, there were about 15,000 such persons [67]. The report on the participants aged 75 years or more does not cite the blood pressure strata, however some information may be extrapolated based on the similar behaviour of systolic pressure in the standard treatment group in both the principal and the 75+ reports of the SPRINT trial [67, 69]. The subgroup analysis according to initial SBP in the entire study group demonstrated that only in the patients from the lowest unattended SBP stratum (< 132 mmHg) a statistically significant reduction of the risk of endpoints was achieved. This finding may in part reflect the fact that this group included the bulk of patients who had their medications tapered down, and that patients from this group would have achieved adequate control of SBP if office values had been substituted for unattended measurements. The closer scrutiny of the blood pressure graphs leads to the conclusion that in the strict blood pressure control group SBP averaged 129.1 mmHg at one month and further fell by 2.5 mmHg by six months and by additional 0.2 mmHg by one year, when it averaged 126.4 mmHg. On the other hand, SBP in the standard treatment group at one month averaged 131.3 mmHg and increased by the time of six-month visit by 0.6 mmHg and by further 0.7 mmHg by one year into the trial, averaging 132.6 mmHg (visual inspection of Figure 2 from reference [67]). Based on the previous research one can assume that the thus produced 6.2 mmHg between-group difference in SBP could have been translated into 16% greater relative risk of all CV events in the standard treatment group compared with the strict blood pressure control group [6]. When corrected according to data published by Filipovský et al. [73], these one year unattended SBP readings would be 141.4 mmHg in the strict control group and 147.6 mmHg in the standard control group. This observation is somewhat in line with the largely negative results of the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive patients (JATOS), in which the reduction of SBP on average to below 140 mmHg did not offer more benefit in older Japanese patients as compared to less strict blood pressure control to below 160 mmHg [76].

After the publication of the SPRINT results, a number of meta-analyses, which included the summary data of this trial appeared. These meta-analyses advocated that SBP should be universally reduced to below 130 mmHg [77–79]. In these reports the sheer weight of the SPRINT group seemed to draw the results towards lower blood pressure goals to be achieved with antihypertensive therapy. However, due to the

aforementioned problems concerning interpretation of the SPRINT trial, despite the sincerity of the effort on the part of the authors of the cited meta-analyses and the investigators of the SPRINT trial, the conclusions to the effect that all our hypertensive patients, irrespective of age, should have their office SBPs reduced to below 130 mmHg seem rather far-fetched. In fact, if data by Lund-Johansen et al. [71], Mancia et al. [72] and recently Filipovský et al. [73] are correct, the SPRINT was a trial assessing the standard control of blood pressure versus no control.

The possible practical answer to the question of the evidence supporting the particular level of SBP, when measured by a physician or a nurse in an office setting, may be supported by the two post-hoc analyses of the INternational VErapamil SR-Trandolapril STudy (INVEST) [80, 81]. An analysis published by Denardo et al. [80] demonstrated that the achieved, on-treatment, SBP at which risk is lowest differs according to patients' age. Whereas, SBP in younger individuals can be safely decreased to below 140 mmHg and no harm is observed at as low values as 120–130 mmHg, in patients older than 70 years of age the lowest risk is noted with the SBP around 140 mmHg and when the achieved values decrease to below 135–140 mmHg, the risk starts increasing [80]. Of note, the U-shaped relation between achieved blood pressure and CV risk was present for both SBP and DBP [80]. Elgendy et al. [81] brought these results a step further. In a report published in 2016 they demonstrated that after maximum of 11 years of extended follow-up for fatal events, the lowest risk for older patients was associated with SBP of between 130 and 140 mmHg, with slightly less favourable results for SBP below 130 mmHg and between 140 and 150 mmHg, and much worse outcomes in patients with SBP exceeding 150 mmHg [70, 81]. However, the analysis by Elgendy et al. [81] is not free of potential flaws, as the blood pressure values on which they base their estimates extended only to 2.7 years of average follow-up.

A recent meta-analysis lent support to lowering of SBP in older hypertensive patients to values below 140 mmHg [82]. The authors demonstrated that such therapy reduces major adverse CV events by 29% (p < 0.001), all-cause mortality by 33% (p = 0.04), and heart failure by 37% (p = 0.04), however this may come at a cost of polypharmacy, and increased risk of such complications as acute kidney injury, hypotension, and syncope [82].

Further evidence came with the publication of data from the Heart Outcomes Prevention Evaluation (HOPE)-3 trial, which indicated that lowering of SBP to less than 130 mmHg with active antihypertensive therapy in intermediate risk subjects, with a mean age of 65.7 and no CV disease, with an exception for individuals with initial SBP values exceeding 143.5 mmHg, did not confer CV benefit [83, 84]. The benefit in these individuals was restricted to the use of rosuvastatin with a marginally greater benefit associated with co-administration of candesartan and hydrochlorothiazide [84].

CONCLUSIONS

The initiation of antihypertensive therapy or its up-titration should be performed carefully in older patients. One should remember that the population of older patients include on one hand generally healthy, biologically younger and fitter individuals, and on the other hand, frail individuals with high degree of comorbidity and polypharmacy. Whereas the former can be approached in a manner in many respects similar to our approaches to younger patients, the latter needs to be addressed more specifically [44]. The importance of the approaches taking into consideration patient's age is wide-ranging. From the issues concerning compliance [85], through potential complications of therapy such as hyponatraemia, hypotension and falls, to a possible inadvertent increase in the risk of CV events in cases where achieved blood pressure would be inappropriately high or inappropriately low [70, 86].

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