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Hypertension in the elderly: Change of, or new implications within the existing, paradigm?

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ABSTRACT

Hypertension is the leading cause of morbidity and mortality among the older adults worldwide. Pathophysiology of hypertension in old age has been linked to the large arterial remodelling and stiffness. This is followed by concentric hypertrophy of the arterioles and baroreceptor dysfunction. The process leads to increase of systolic (SBP) and, after 5th decade, decrease of diastolic (DBP) blood pressure, with the bulk of the hypertension-related risk associated with SBP rather than DBP. However, the exact SBP value that should constitute the threshold for the diagnosis of isolated systolic hypertension has been debated. On one hand, a constant and linear relationship between systolic blood pressure and risk of complications has been implied. On the other hand, some experts point to the possibility of age-stratified cut-off values. When assessing the results of outcome trials in especially the oldest old, the absolute benefit is of paramount importance, when a greater relative benefit does not necessarily translate into less patients who need to be treated for a given period of time to avoid one event, and remaining life expectancy may be less than ten years. The latter issue is also of importance when generalisability of the clinical trial results is concerned. Further, especially in patients aging without success, burdened with multiple chronic diseases and poorly functioning, we need to take into account the average remaining life expectancy, their cognitive and functional capacity, comorbidities, polypharmacy together with patients' preferences. Whenever possible, a "de-prescribing" model of hypertension management in old adults may have some merit.

1. Introduction

Despite the long track of excellent research and all the evidence gathered therefrom, hypertension in the older patients is far from being a fully settled issue. From pathophysiology, through relationship between blood pressure level and the risk, the cut-off for diagnosis to therapeutic goals, the discussion of different standpoints is still ongoing. Even the choice of preferred medications to be used to treat hypertension in older patients has been differently addressed by different sets of guidelines published across the World. Some other issues related to hypertension in the older patients have only recently been properly addressed at the level of expert consensus or guideline documents, with hypertension in the very old frail patients coming as a fitting example. The problems with the generalisability of the clinical trial results impose the need to implement the results of clinical trials only after appropriate consideration of benefits and potential risks associated with novel approaches in what is a heterogeneous group of patients.

2. Pathophysiology

Hypertension is the leading cause of morbidity and mortality among adults worldwide [1,2]. The epidemiologic data indicate that the majority of cases arise in the older persons. It has been estimated that the remaining lifetime risk of becoming hypertensive reaches 90% for a subject reaching the age of 55 years [3,4]. The core pathophysiologic problem in essential hypertension regardless of patient's age is dysregulation as described decades ago by Irving Page [5]. However, the pathopysiology of hypertension in the older persons differs in many ways from the one we encounter in younger subjects. Due to widespread remodelling and ensuing stiffening of large arteries, the ageing aorta looses part of its elastic properties [6,7]. This in turn, translates into higher systolic (SBP) and lower diastolic (DBP) blood pressure in ascending aorta, and faster propagation of the forward and reflected pressure pulse waves along the arterial tree. The latter phenomenon leads to further increase in SBP and lack of kick to DBP in ascending aorta

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which directly translates to greater afterload, and poorer left ventricular perfusion [7–9]. It also leads to greater oscillations between SBP and DBP, usually referred as to pulse pressure (PP) [8], a repetitive "hammering" force, further leading to large arterial damage and remodelling [8,10]. The changes do not stop at the level of large arteries, as the arterioles when facing increased SBP undergo concentric hypertrophy [9]. This compensatory mechanism in its turn is in part responsible for an increased peripheral resistance, further leading to increase of blood pressure. Also, the baroreceptor function diminishes with ageing and ensuing carotid atherosclerosis, [6,9] which further adds to the mechanisms behind elevation of blood pressure in the older patients.

3. Epidemiology

Currently, based on epidemiologic and clinical trial data, it has been widely acknowledged that the bulk of the hypertension-related risk in older patients is associated with SBP rather than DBP [11,12]. Many published data indicate that there should exist a constant linear relationship between blood pressure and risk of complications which is observed in all adults irrespective of their age [13,14]. For SBP this relationship starts at the level of 115 mmHg. This has been supported by an analysis which included a large cohort of subjects drawn from general population [11,15–17]. However, the exact systolic blood pressure value that should constitute the threshold for the diagnosis of isolated systolic hypertension (ISH) has been debated [18,19]. The guidelines state that the ISH can in general be diagnosed when the SBP is equal or greater than 140 mmHg and the DBP is less than 90 mmHg, irrespective of patients age [19]. However, several important analyses show that the level of SBP from which risk starts rising sharply is different for patients at different age. A reanalysis of data from the Framingham Heart Study, showed that whereas the threshold for men aged 45–54 can be set at 140 mmHg, for men aged 65–74 it increases to approximately 160 mmHg, with even greater values for women of respective ages [20]. Another insight comes from blood pressure – outcome relation based on on-treatment blood pressure data coming from large clinical trials. By far and large most important of such data come from the INVEST trial [21,22]. The first of the two analyses investigated the age-stratified risk of mortality associated with systolic and diastolic blood pressure at the end of the trial [21]. It showed that whereas for adult patients aged up to 69 years the systolic blood pressure can be reduced to approximately 120 mmHg and confer benefit to the patient. However, in patients aged 70 years and more, the SBP-risk relationship was negative starting from SBP of approximately 140 mmHg downwards [21]. The second analysis was based on an extended, 11 year observation of the study cohort, which makes it the longest follow-up for survival among clinical trials in hypertension [22,23]. The important contribution by Elgendy et al. has potentially far-reaching practical consequences. For patients < 60 years of age with coronary artery disease, the SBP of 130 to 140 mmHg is the most beneficial value, with no additional risk reduction when lowering the BP further and with significantly less benefit at higher SBP levels. However in individuals of 60+ years, the optimum SBP would be between 130 and 140 mmHg. Patients with follow-up SBP < 130 mmHg and with follow-up SBP between 140 and 150 mmHg faring equally well but significantly worse than the 130 to 140 mmHg group, and the patients with follow-up SBP > 150 mmHg faring much worse [22].

4. Therapeutic intervention –evidence beyond relative risk reduction

It has been the common practice to present the results of outcome trials in terms of relative risk reduction, and only as an addition to cite the absolute benefit. However, especially for the very old (octogenarian or older), whose average remaining live span is counted not in decades but years (10 years on average for a person aged 80 years) [24], the presentation of the results in terms of the extent of absolute benefit is of paramount importance. The absolute benefit is usually presented as number of patients who need to be treated with favourable regimen for certain number of years, usually five, to avoid one outcome event [25]. Paradoxically, in case of many studies and particular events, greater relative benefit does not necessarily translate into less patients who need to be treated for a given period of time to avoid one event. Therefore, below, we put stress on the absolute benefit displayed in discussed trials.

Thus far three major, adequately powered, placebo-controlled clinical trials were performed, which investigated whether the antihypertensive treatment of older patients with isolated systolic hypertension would be beneficial. These included the Systolic Hypertension in the Elderly Program (SHEP) [16], the Systolic Hypertension in Europe (Syst-Eur) [15], and the Systolic Hypertension in China (Syst-China) [26] trials. The primary outcome measure of SHEP, Syst-Eur and Syst-China, was stroke, and in all of these trials it was significantly reduced. In all these trials patients were included if their SBP was at or greater than 160 mmHg. After the follow-up of 2–4 years the relative risk of stroke in the actively treated groups was 36–42% (all $P < 0.01$) less relative to placebo groups. Notably, the number of patients who needed to be treated for 5 years to prevent one stroke ranged from 20 in SHEP [16], 25 in Syst-China [26], to 34 in Syst-Eur [15]. Overall, based on results of a meta-analysis of individual patient data from clinical trials of antihypertensive therapy in the older patients with ISH, it was proven that the treatment of ISH of > 160 mmHg in patients aged 60+ is beneficial. Overall the analysis confirmed that over median of 3.8 years of follow up, 1 mmHg treatment-induced decrease in SBP translated to approximately 2.5% less relative risk of all cardiovascular events combined [11].

5. Special groups of patients/issues

Since the publication of data supporting therapy of the so-called essential, isolated systolic hypertension, with SBP level exceeding 160 mmHg in patients at or above the age of 60 years, there has been a debate as to whether this benefit would extend to the population of patients above the age of 80 years. An influential individual patient data meta-analysis by Gueyffier et al. [27] showed, that although octogenarian patients actively treated for hypertension did encounter definite benefit concerning stroke and other cardiovascular events, there was no difference relating to mortality. Despite of the lack of statistically significant difference in relative risk of total mortality, the authors stated that there had been a non-significant trend towards more fatal cases in the active treatment group of 6 (−5 to 18)%. On the other hand, when looked upon from the absolute perspective, the between group difference in total mortality amounted to 0% (28% of both samples died during the follow-up). The peculiar feature of the included age group was that there were more deaths than all other events combined. This further underlines the lack of any excess of mortality in the actively treated group [27].

These results prompted the idea for the HYVET trial [17]. HYVET was double-blind, randomised, placebo controlled trial of active antihypertensive treatment based on thiazide-like diuretic indapamide and a long-acting angiotensin converting enzyme inhibitor (ACE-i) perindopril. To be eligible for inclusion a patient had to be at least 80 years of age, have essential hypertension with SBP of 160 mmHg or more, not had had a haemorrhagic stroke in the 6 months prior to enrolment, have serum creatinine below