

Blood pressure targets in the elderly

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Several factors surrounding the treatment of hypertension have continually caused controversy over the last decades and remain unresolved. Key examples of these issues include choice of first-line antihypertensive therapy, the role of combination therapy, blood pressure (BP) in the context of other cardiovascular risk factors and the role of assessment of subclinical and overt organ damage in defining treatment strategies. Nothing, however, has stimulated debate to the extent seen over BP targets.

Contemporary guidelines generally advocate lower BP targets compared with earlier recommendations when hypertension was first recognized as an important yet modifiable cardiovascular risk factor. The issue is further illustrated by more sophisticated classification of BP not only in the hypertensive range but also within normotensive values; concepts such as 'prehypertension' and 'high normal blood pressure' illustrate that there could be an optimal BP range that is lower than the current diagnostic threshold of 140/90 mmHg. Discussions about J-shaped and U-shaped curves that describe the relationship between BP and cardiovascular risk are important in this context and have been revisited many times over the years. It has indeed been recognized that comorbidities such as diabetes and renal failure may mandate different and often lower BP targets compared with the general population as a result of altered relationships between BP and cardiovascular risk in these high-risk patients [1]. Studies that specifically address the question of optimal BP targets such as Hypertension Optimal Treatment [2] and more recently SPRINT [3] have therefore attracted widespread attention but also critique [4]. It is probably fair to say that there is still debate on optimal BP targets but that a 'the lower the better' concept is generally accepted for most patients.

It therefore came as a surprise to the hypertension community when the Eighth Joint National Committee

(JNC 8) defined a higher BP target for people above the age of 60 years [5]. Of course the decision to recommend a target of 150/90 mmHg was well justified by the committee and based on the existing literature, applying a new and rigorous pipeline to examine the existing evidence, in keeping with Institute of Medicine recommendations. However, the 150/90-mmHg target in the elderly was still a decision against the general 'the lower the better' trend. And it was not accepted by all committee members; opponents of this target published a 'minority report' outlining their views and interpretation of the evidence in more detail compared with the statements in the JNC 8 report [6].

There are good reasons to define different BP targets depending on comorbidities, organ damage, sex and age to take specific pathophysiological mechanisms and cardiovascular risk in different groups of patients into account. In the elderly, it has repeatedly been argued that low BP could lead to dizziness and orthostatic reactions, thereby increasing the risk of falls and fractures [7]. It has also been argued that increased vascular stiffness in the elderly which results in lower diastolic pressure and higher pulse pressure would require different BP-lowering strategies compared with younger patients [8]. In addition, one of the largest BP trials available at the time of the JNC 8 process, the Hypertension in the Very Elderly Trial, specifically looked into a 150/80-mmHg target [9]. Nevertheless, there have been concerns that a more relaxed BP target in the elderly would lead to undertreatment of those who may benefit most from anti-hypertensive therapy and that JNC 8 has sent out a 'wrong' message to the clinical community [6].

The current discussion about 10 mmHg in the elderly is of course only a continuation of the general debate on BP targets that we have witnessed for many years. There will be no absolute 'right' or 'wrong' and it is well possible that this recommendation, not unlike other recommendations, will be updated and modified in future editions of the JNC guidelines. In fact, to some extent the discussion in 2014 does not fully apply to the situation in 2017 in which SPRINT has shown benefits of more intensive BP treatment also in the elderly [3]. One should also bear in mind that guidelines indeed provide general guidance but that treatment decisions in individual patients will always be driven by person-specific factors based on the clinical picture and experience of the physician. There is a fine balance between an abstract population benefit of tight BP control (that can of course also translate to individual benefits) and the concrete adverse effects in individual patients including

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dizziness, falls risk, risk of renal failure and electrolyte disturbance and generally polypharmacy – particularly in the elderly. However, this concept is not specific to the elderly, and treatment decisions will always be tailored to the individual with guidelines providing, indeed, only guidance.

In this issue of the *Journal of Hypertension*, we find further data on BP targets in the elderly in an article by Naylor *et al.* [10]. The authors have modelled in two large general population cohorts, the Framingham (FHS) and Jackson Heart Studies (JHS), the incidence of cardiovascular events in people above the age of 60 years with BP (treated or untreated) in the range of 140–149 mmHg systolic and less than 90 mmHg diastolic. Compared with people without hypertension, their risk was consistently higher, and this risk extended to those aged 60 years and older. The authors conclude that treatment to JNC 8 recommendations in the elderly, aiming at BP below 150 mmHg systolic, is associated with substantial residual risk of cardiovascular events.

Such epidemiological data have been available for many years. For example, the Prospective Studies Collaboration showed direct relationships between BP and cardiovascular risk across all ages and levels of BP [11], and there are other large-scale population studies that have fuelled the discussions on BP targets in recent years. In fact, an analysis by Bavishi *et al.* [12] along the same lines as the data provided by Naylor *et al.* arrived at very similar conclusions. Such data will always have to be interpreted with caution as they do not derive from randomized controlled trials, but they can inform the discussion. In this sense, the data by Naylor *et al.* [10] are important albeit probably not surprising. They have, however, been derived from contemporary US American population cohorts and should have particular relevance to the JNC that in the first instance addresses the situation in the United States of America.

We recommend the reader to critically assess the evidence provided in the article by Naylor *et al.* [10]. There are strengths and weaknesses but in the light of decades of discussions on BP targets it cannot be the task of this editorial to add further arguments. The data in the article by Naylor *et al.* are clear and well presented and appear to support the notion that 150/90 mmHg is too high a threshold for initiation of antihypertensive therapy and too high a treatment target in the elderly.

A few issues in the article by Naylor *et al.* [10], however, deserve special attention. First, the data derive from two cohorts with different BP measurement protocols. We have seen in the post-SPRINT discussions how important the exact measurement protocols can be, depending on the method used the actual measured BP can differ by several, maybe up to 10 mmHg. Even tiny BP differences only occurring during certain phases of a trial can result in differences in cardiovascular outcomes as the Valsartan Antihypertensive Long-term Use Evaluation trial has painfully demonstrated [13]. We do not know if the FHS and JHS data can be meaningfully combined, even if the meta-analysis approach and the provided sensitivity analyses offer some reassurance. Second, not much is known about the details of antihypertensive therapy in the FHS and JHS participants – when was the therapy initiated, why was it initiated, what targets were defined for individual patients

by their physician, what (e.g. adverse effects) has driven a change in therapy? It should also be noted that BP targets will have generally changed over decades in parallel to updated guidelines. All this information would be important beyond the simple numerical BP values that have been used for the present analysis by Naylor *et al.* [10]. In addition, third, this analysis has been performed with the benefit of hindsight but not as a prospective clinical trial. It is somewhat easier to explore existing datasets than to set up a prospective clinical trial to more robustly answer a clinical question, and as with every secondary or not predefined analysis, there is a risk of both false positive and false negative findings.

We would like to leave the exact interpretation of the data by Naylor *et al.* [10] to the clinical community and to future guideline committees. Instead we would like to put this article into the current precision medicine landscape and see it as a wake-up call for the hypertension community to generate better and more detailed data [14,15]. As valid as the analysis of a relationship between BP level and outcome may be on the population level or in the context of large clinical trials, the treatment of individual patients often requires information beyond such simple data. We have already mentioned such factors including duration of hypertension, adverse effects, degree of organ damage and comorbidities above, and they can be supplemented by biomarkers, genetic and genomic information and other factors that stratify patients into specific groups with regard to risk and treatment options. In fact, this information has the potential to define individual subtypes of hypertension and characterize the phenotype far better than the numbers that we read on a sphygmomanometer.

Such information is not available in the present analysis of FHS and JHS data by Naylor *et al.* [10] and in all fairness, is not available in any of the larger population based and clinical trial datasets. The best we can currently do is indeed what Naylor *et al.* have done: to analyse BP figures against defined outcomes, adjusted for the available relevant clinical data. We thereby reduce a complex phenotype to a readout and miss opportunities to define tailored treatments for individual patients or patient groups. In the case of the elderly, this is not only a question of missing molecular (biomarker, genetics) data but very much also a question of stratification by sex in which one would expect differences in the pathophysiological make-up of hypertension in postmenopausal women who ‘catch up’ with their cardiovascular risk compared with men who have different onset and development of high BP. By simply adjusting for sex, we cannot answer such fundamental questions in existing datasets.

In summary, the article by Naylor *et al.* [10] provides data that inform the discussion on BP targets, but even more importantly, it provides food for thought for the design of future clinical trials and general population cohorts. The experienced team of Naylor *et al.* has carefully analysed the available datasets using sophisticated statistical methods and are still limited by the missing phenotypic depth of these datasets. If we really want to enter the precision medicine age also for the diagnosis and treatment of hypertension, we have to generate deeper phenotypic data and will then, hopefully, be able to answer questions about BP

targets and all the other controversies that the hypertension community has struggled to answer for so many years.

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Conflicts of interest

There are no conflicts of interest.

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