Controversies in the management of patients with arterial hypertension

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Short title: Controversies in hypertension management

Abstract
Every 5 to 6 years, international and national guidelines provide updated recommendations for the standard management of hypertension in adults. Thus, within the last 18 months, European (ESC/ESH), American (ACC/AHA) and British (NICE) societies published their new guidelines. Despite the fact that all of them are supposedly based on most recent clinical evidence, there are always some discrepancies between recommendations due to different interpretations of the clinical trials. The purpose of the present review is to discuss six issues that have generated some controversies. These address the definition of hypertension, the identification of who should be treated, the target BP to achieve, the pertinence of reducing salt intake and the actual place of renal denervation in resistant hypertension.

Key words: blood pressure, classification, targets, single pill combination, renal denervation, sodium
**Introduction**

Hypertension is the main risk factor for the development of cardiovascular diseases worldwide affecting now more than 1 billion persons worldwide and reducing blood pressure (BP) in hypertensive patients is the most effective way to lower the mortality and target organ damages associated with hypertension [1]. Today, these two allegations are well accepted in the medical community but this has not always been the case. Indeed, in the midst of the 20th century, many physicians were considering arterial hypertension as a compensatory mechanism that did not deserve any treatment, whereas others were proposing drug treatments for those with an elevated BP without the strong support of clinical trials. This was probably the first important controversy in the management of essential hypertension. In the 1960ies and 70ies, the first randomized controlled trials conducted by the Veterans Administration Cooperative Study Group confirmed the benefits of treating patients with elevated diastolic BP [2, 3]. Consequently, the first Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure published in 1977 a strict recommendation to treat any hypertensive patient with a diastolic BP > 115 mmHg and to consider therapy in those with a diastolic > 90 mmHg depending on their cardiovascular risk (JNC1)[4]. In the same decade, the first guidelines for the management of hypertension were issued first by the World Health Organization (WHO) and the International Society of Hypertension (ISH) and thereafter by the JNC with the objective to help physicians in their clinical decisions [5]. “Hypertension experts” wrote these guidelines, updated periodically. Until 2003, the European Society of Hypertension (ESH) and that of Cardiology (ESC) endorsed the WHO/ISH guidelines but thereafter they considered that these guidelines might not be representative because of the heterogeneity of countries with variable accesses to health care and drug therapies, and different economic resources. Therefore, they started to publish their own guidelines in 2003 introducing progressively evidence-based criteria.
Simultaneously, several countries started to publish their own national recommendations [6]. These latter were sometimes but not always in accordance with international guidelines coming from the United States or from Europe, leading to controversies on how to manage hypertensive patients. In this respect, the recently published guidelines from the ESC/ESH [7] in Europe and from the ACC/AHA [8, 9] in the US and even more recently the 2019 NICE guidelines from Britain (https://www.nice.org.uk/guidance/ng136) did not escape the tradition with some substantial differences generating animated controversies. The purpose of this article is to discuss some of the recent controversies in the diagnosis and management of hypertension in adults according to the most recent recommendations.

1. **The definition of hypertension: is \(140/90\) mmHg still correct?**

The major actual controversy in the field of hypertension concerns the definition of hypertension. Hypertension in adults is defined as a BP \(\geq 140/90\) mmHg with a special consideration for elderly patients with isolated systolic hypertension defined as a systolic BP \(\geq 140\) mmHg but a diastolic BP < 90 mmHg. This definition is accepted and applied worldwide since decades. In 2018, the ACC/AHA guidelines changed this definition putting the cut-off between normotension and hypertension at 130/80 mmHg [8, 9] (Table 1). In addition, subjects with a systolic BP between 120 and 129 mmHg and a diastolic BP < 80 mmHg have an elevated BP. This major modification has generated many negative reactions for several reasons. Firstly, it increased by almost 15% the number of hypertensive subjects in the population; secondly, it also increases the percentage of treated hypertensive patients with uncontrolled hypertension and thirdly, it raises substantially the number of patients with a low cardiovascular risk needing a clinical management by general practitioners with the risk of inducing more side effects than clinical benefits. Interestingly, in the United States, the American Academy of Family Physicians and the American College of Physicians
refused this modification. Thus, we have now an heterogeneous definition of hypertension and this might have harmful consequences on the global management of hypertension in the population because it adds confusion in physicians’ and people’s mind [10].

The main reason why the ACC/AHA guidelines committee changed the definition of hypertension is due to the results of the Systolic Blood Pressure Intervention Trial (SPRINT) published in 2015 [11]. In this trial, targeting a systolic BP of < 120 mm Hg, as compared with < 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause. Moreover, the benefits of reaching the lower target were also present in elderly [12]. However, the major issue in SPRINT is the method used to measure office BP during the trial. Indeed, in contrast to all previous clinical trials in hypertension, SPRINT investigators used a different methodology combining an automated device with measurements done in a quiet room unattended or unobserved—that is, without an observer being present in the room [13]. Thus, the treatment arm < 120 mmHg in SPRINT very likely compares with higher systolic BP values when measured in a classical physician’s office. This was actually demonstrated by Filipovski et al who reported a 8.5 ± 9.0/3.0 ± 6.1 mm Hg lower office BP when measured unattended with an automated device as compared to the classical auscultatory method [14].

With these new information in hands, what should practitioners do? Most national hypertension guidelines in Europe (including the very recent NICE guidelines) and Asia [15] have actually maintained the 140/90 mmHg cut-off defining hypertension. This is true also for Poland [6, 16]. This seems reasonable as long as office BP is measured using either auscultatory or oscillometric devices in the presence of a physician or a nurse. Physicians could apply the ACC/AHA definition only if they modify their habits and start measuring BP according to the SPRINT protocol i.e. with an automated device, in a quiet room and without any healthcare professional in the room (unattended).
2. **Who should be treated?**

So far, there is no strict recommendation to treat patients with high-normal BP, i.e. with BP values between 130-139 mmHg systolic and 85-89 mmHg diastolic. At best, guidelines suggest to follow these subjects regularly and to implement lifestyle changes if necessary. In support of this attitude, the HOPE-3 trial confirmed that drug therapy is not associated with a lower rate of major cardiovascular events than placebo among this category of patients with an intermediate risk and no cardiovascular disease, unless systolic BP is > 143 mmHg [17]. According to the 2017 ACC/AHA guidelines, these patients would be considered as hypertensive and should receive lifestyle recommendations and a medical treatment if BP remains >130/80 mmHg. The 2018 ESC/ESH guidelines have now made a step in the direction of American recommendations in that, subjects with high-normal BP should receive drug treatment if their calculated cardiovascular risk is greater than 5% (high and very high CV risk patients) or if they have renal disease or hypertension-mediated organ damages [7]. This novel attitude towards patients with borderline BP values emphasize the need to estimate more systematically the cardiovascular risk profile of all patients in whom BP is measured. A specific cardiovascular risk assessment system and risk charts calibrated for Polish population has been published in 2015 [18].

3. **Treating hypertensive patients: how low should we go?**

In the majority of guidelines, the general recommendation is to lower BP < 140/90 mmHg implementing first lifestyle changes and then introducing drug therapies. Exceptions in treatment targets exist in some guidelines for very elderly (<150/90 mmHg) or patients with diabetes or chronic kidney disease and proteinuria (<130/80 mmHg) or patients with coronary artery disease (<130 mmHg). In coherence with their new classification, 2017 ACC/AHA
guidelines recommend to lower BP below 130/80 mmHg and this whatever the age and concomitant diseases. This new approach based again on the results of the SPRINT trial and some, but not all, meta-analyses has raised up many comments. First, this low target will be difficult to achieve in many patients if one considers that today, less than 50% of treated hypertensive patients achieve a target BP < 140/90 mmHg. Therefore, it may be very discouraging for both patients and physicians. Moreover, there is no evidence from randomized controlled trials to support a diastolic BP of < 80 mm Hg. In addition, in some patients, like elderly, a more intensive treatment to reach the low target may be rather harmful. Indeed, in the SPRINT trial patients randomized to the 120 mmHg systolic BP target experienced more frequently hypotensive episodes and worsening of renal function [11]. At last, this low target might increase the number of consultations needed to manage hypertensive patients in practice and hence overload most general practitioners. Therefore, it appears more reasonable to apply the target strategy recommended by the ESC/ESH guidelines [7], which provide a range of targets to obtain in two steps. The first is to bring BP below 140/90 mmHg in all hypertensive patients. Then, BP can be lowered further to 130-140 mmHg in most patients depending on their age, level of cardiovascular risk, tolerance to the hypertensive therapy and the presence or absence of concomitant diseases.

4. Starting drug therapy: monotherapy or single pill combinations first?
Step-care drug therapy has been the standard of care in hypertension since the very first hypertension guidelines in the 1970ies. Today, it remains the most recommended therapeutic strategy in most guidelines. Thus, ACC/AHA guidelines recommend to start with a monotherapy in patients with stage 1 hypertension whereas in stage 2 hypertension initiation of antihypertensive drug therapy with two first-line agents of different classes, either as
separate agents or in a fixed-dose combination, is recommended. A similar approach is proposed in Polish guidelines [16]. According to the 2019 NICE guidelines, physicians should offer an ACE inhibitor or an ARB monotherapy as step 1 to adults who have type 2 diabetes and are of any age or family origin or are aged under 55 years but not of black African or African–Caribbean family origin. Patients should receive a calcium-channel blocker (CCB) monotherapy as first step 1 antihypertensive treatment if they are aged 55 or over and do not have type 2 diabetes or if they are of black African or African–Caribbean family origin and do not have type 2 diabetes (of any age) (https://www.nice.org.uk/guidance/ng136/chapter/Recommendations) (verified September 27th 2019).

The guideline committee of ESC and ESH have decided to modify their therapeutic strategy for several reasons. Firstly, the step-care therapy has now been used for decades with a modest success rate in controlling hypertension. Indeed, in most European countries the control rate of treated patients does not exceed 50%. Secondly, 40 to 50% of treated patients stop their antihypertensive therapy during the first year because of the pill burden. Thirdly, many physicians do not adapt the patients’ therapy after the prescription when BP is uncontrolled. Fourthly, the time needed to obtain an adequate BP control is often very long (> 6 months). Thus, the objective of the strategy change was to increase the BP lowering efficacy of the first step, to reduce the pill burden and to shorten the time to BP control. To achieve these goals the ESC/ESH guidelines recommend to start antihypertensive with a single pill combination of two drug classes, i.e. a blocker of the renin-angiotensin system (RAS) combined with a diuretic or a calcium channel blocker. The second set consists in prescribing a single pill triple combination associating the RAS blocker, the diuretic and the calcium antagonist. This more aggressive initiation of therapy should enable to control BP in 50 to 60% of patients after the first prescription of a single pill. Yet, the use of a monotherapy
as first step is not completely abandoned but it is reserved to frail very elderly patients or to
younger patients with a modest elevation of BP. This new therapeutic approach was generally
well received but its implementation may encounter obstacles in some countries, as dual and
triple single pill combinations are not universally available or reimbursed.

5. **Lifestyle changes: should sodium intake be reduced and how much?**

Physiologically, sodium is one the main determinant of blood pressure. Several
epidemiological surveys have demonstrated that the higher the salt intake in populations, the
higher the blood pressure and the risk of developing hypertension with age [19-23]. There is
also a relationship between sodium intake and the risk of death and cardiovascular events [19,
23-26]. However, some investigators found a linear correlation between sodium intake and
cardiovascular events [24, 25] whereas others reported an increased risk of death and
cardiovascular events at higher as well as at lower estimated level of sodium intake,
suggesting a U shaped relationship [26, 27]. Therefore, the authors of these latter
observations do not support the recommendations made by the WHO, the American Heart
Association or the ESC/ESH to reduce sodium intake in populations to 1.5-2.0 g sodium per
day or 5 g NaCl per day. These apparently contradictory results have generated a strong
controversy in the cardiovascular community, some supporting a general reduction in salt
intake in populations and others suggesting not changing anything. For many years, the
reasons for the discrepancy was not well understood except for the fact that spot urine
samples rather than 24h urine collections were used to estimate sodium intake in studies
reporting a U-shaped relationship. Very recently, He et al re-analyzed the Trials of
Hypertension Prevention follow-up data [28]. They calculated sodium intake using the
measured 24-hour urinary sodium excretion as well as the estimations from spot sodium
concentrations using the Kawasaki, Tanaka, and INTERSALT (International Cooperative
Study on Salt) formulas. Their analysis suggests that the U-shaped relationship is due to an artefact associated with the use of spot urine samples, which take into account sodium as well as creatinine [28]. Therefore, they concluded that inaccurate estimates of sodium intake (with formulas based on a spot urine) cannot be used in association studies, as the formulas per se seem to be related to mortality independent of sodium [28]. Whether this finding will close the dispute is unknown, but it will unlikely be the case.

Nevertheless, salt consumption is high in most countries of the World. Thus, the estimated mean level of global sodium consumption was 3.95 g per day (or 10g NaCl per day) in Mozaffarian’s survey [23] but with regional mean sodium levels ranging between 2.18 and 5.51 g per day. In this survey, countries from central and eastern Europa belonged to those with the highest sodium intake. Thus, it is wise to recommend a general reduction of sodium intake in these populations, which include Poland. At this point, it is useful to remember that in hypertensive patients, lowering salt intake is beneficial in several aspects: not only it lowers BP and cardiovascular events but it also increases the antihypertensive efficacy of RAS blockers and diuretics and lowers microalbuminuria. At the 2019 ESC meeting in Paris, Dr Jaime Miranda from Lima presented the results of their prospective study in Peru, in which they replaced the normal sodium chloride by a salt substitute containing 75% sodium and 25% potassium in the households of 6 Peruvian villages [29]. The substitution induces modest decreases in BP in the population but the most striking result was that the salt substitute significantly reduced the likelihood of developing hypertension by 51% compared to using normal salt (hazard ratio 0.49; 95% confidence interval 0.34–0.71; p<0.001) (https://www.escardio.org/The-ESC/Press-Office/Press-releases/community-based-salt-substitution-programme-lowers-blood-pressure). Thus, these data suggest that lowering salt intake in the population may prevent the development of new cases of hypertension.

Therefore, even though they may still be some controversy on the pertinence of reducing salt
intake to 5-6 g day, salt reduction appears to be a wise recommendation, at least for patients with hypertension.

6. **Resistant hypertension and renal denervation: still alive?**

The development of device therapies such as renal denervation (RDN), baroreflex activation therapy and endovascular baroreflex modulation has stimulated the clinical interest and the research in the field of resistant hypertension. Indeed, these devices were originally designed to improve the management of patients with severe uncontrolled hypertension and hence, this promoted much research on the prevalence and clinical characteristics of resistant hypertension.

Several surveys have been conducted to determine the prevalence of resistant hypertension [30-33]. Interestingly, large discrepancies were found in these studies with prevalence ranging between 5 and 30%. In fact, after excluding the cases of pseudo-resistant hypertension due to non-adherence to drug therapy and white-coat hypertension, the prevalence of true resistant hypertension was much lower, below 5% in the general population and slightly higher in hypertension centers where complicated cases are referred [34]. The second observation is that many patients with resistant hypertension can actually be controlled using the prescription of spironolactone as fourth line therapy after diuretics, calcium antagonists and RAS blockers [35-38]. Thus, the real need for an interventional therapy decreased significantly as more precise information on resistant hypertension were gathered.

The initial clinical and experimental studies using radiofrequency RDN to reduce BP in resistant hypertension were quite promising [39, 40], but the enthusiasm fell after the publication of the negative results of Symplicity HTN-3 [41], which lead to a drastic reduction in the number of procedures performed around the world. Nevertheless, some
device companies did not stop their programs and rather started new ones with revised objectives. New goals were to demonstrate that RDN indeed lowers BP in other groups of patients, to refine the technology in order to apply the denervation more distally in renal arteries, and to reduce the variability of the response to RDN improving the selection of patients who could benefit from the therapy. Two clinical programs should be cited i.e. the SPYRAL and the RADIANCE study programs. These programs addressed different populations such as untreated hypertensive patients and new technologies such as ultrasounds as reviewed recently by Lobo et al [42]. Several of these studies confirmed the antihypertensive efficacy of RDN when compared to a sham procedure as illustrated in Figure 1 [43-45]. In addition to these studies, several registries were created to collect the multiple local experiences. The first results of these registries actually support the conclusions of the trials [42]. However, according to the 24h ambulatory BP data, the BP lowering effect of RDN appears to be modest, equivalent to the efficacy of one antihypertensive drug. Moreover, the response to RDN remains unpredictable and it is almost impossible to define a priori the good candidates to RDN. Thus, taken together, these results confirm that renal denervation lowers BP but, at the present time, this approach cannot be recommended for a routine use. However, it might be proposed to patients with a severe hypertension despite a high number of prescribed drugs or to non-adherent patients who refuse antihypertensive drugs, but in many of these patients, RDN per se will not be sufficient to control BP adequately. Several studies are still ongoing and physicians may have to wait for a better positioning of this approach in the management of hypertensive patients.

Conclusion
This article briefly discuss six major points of controversy being discussed today in the field of arterial hypertension. In the last pages of the 2018 ESC/ESH hypertension guidelines,
there is a list of 26 topics for which there are major gaps in evidence and additional studies are needed [7]. Each of this topic could represent a matter of controversial debate. In the absence of sufficient evidence, physicians must decide according to their own experience in the best interest of their patients. In this respect, the best interest of a patient with hypertension is often to have a well-controlled blood pressure.
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Table 1: Definition of hypertension categories according to ESC/ESH guidelines 2018 and ACC/AHA 2017 guidelines

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<td>Systolic</td>
<td>Diastolic</td>
<td>Systolic</td>
<td>Diastolic</td>
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<td>Optimal</td>
<td>&lt;120 and</td>
<td>&lt;80</td>
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<tr>
<td>Normal</td>
<td>120-129 and/or 80-84</td>
<td>Normal &lt;120 and &lt;80</td>
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<tr>
<td>High normal</td>
<td>130-139 and/or 85-89</td>
<td>Elevated 120-129 and &lt;80</td>
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<tr>
<td>Grade 1 Hypertension</td>
<td>140-159 and/or 90-99</td>
<td>Stage 1 130-139 or 80-89</td>
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<tr>
<td>Grade 2 Hypertension</td>
<td>160-179 and/or 100-109</td>
<td>Stage 2 ≥140 or ≥90</td>
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<tr>
<td>Grade 3 Hypertension</td>
<td>≥180 and/or ≥110</td>
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<tr>
<td>Isolated systolic Hypertension</td>
<td>≥140 and ≤90</td>
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*Note: ESC/ESH = European Society of Cardiology/European Society of Hypertension, ACC/AHA = American College of Cardiology/American Heart Association.*
**Figure 1**: 24 hour ambulatory systolic blood pressure reduction in SPYRAL HTN-OFF MED and HTN-ON MED, RADIANCE-HTN SOLO and SYMPLICITY HTN-3 randomized clinical trials. (from ref 42 with permission).