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Review

Changes in blood pressure classification, blood pressure goals and pharmacological treatment of essential hypertension in medical guidelines from 2003 to 2013

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ABSTRACT

This article aims to discuss differences in pharmacological treatment through a period of 10 years from 2003 to 2013. Hypertension treatment faces many challenges because of patients' unawareness and adherence, clinical inertia, as well as rapid availability of new medical literature and trials. Since 2003, JNC 7 was published at nearly the same time with ESC/ESH Guidelines and WHO/ISH Statement on management of hypertension [1–3]. However, these guidelines are not homogenous in pharmacological therapy approach. Moreover, during the 10 years since 2003, many new large trials, data, and updated guidelines have resolved some main controversial problems in blood pressure (BP) goals in separate risk-categorized patients, levels of BP for initial antihypertensive therapy, choice of drugs in monotherapy, indication for drug combinations, and preferred combinations for special cases. The latest updated guidelines on hypertension treatment, 2013 ESC/ESH Guidelines for the management of arterial hypertension, not only contain significant changes in the abovementioned problems, but also raise some new questions for the future research [4].

1. Blood pressure classifications

In 2003, some important observational studies were acknowledged and considered as key data for the JNC 7 new blood pressure classification (Table 1) [1]. Indeed, the "normal" BP range in the JNC 6 or other previous guidelines was not proved to be normal [5]. A meta-analysis of one million adults from 61 prospective studies demonstrated that mortality rate of ischemic heart disease (IHD) and stroke linearly rose when the SBP values above 115 mm Hg and DBP values greater than 75 mm Hg were observed [6]. This finding was also confirmed by the Framingham Heart Study, in which individuals with BP values between 130–139/85–90 mm Hg had two-times higher cardiovascular disease (CVD) relative risk in comparison with one whose BP values were below 120/80 mm Hg [7]. In addition, in a WHO report, the previously defined suboptimal BP (SBP > 115 mm Hg) range was linked with 62% of cerebrovascular disease and 49% of IHD [8]. According to this data, the definition of "prehypertension", which was not considered as a disease category, was mentioned for the first time in JNC 7 with the claim that the earlier the control of BP by healthy lifestyle, the greater reduction in BP values as well as the slower the progression of hypertension [1]. Also, in JNC 7, Stage 3 hypertension was no longer used since it and Stage 2 hypertension had similar management strategies [1]. New JNC has not been published yet, and JNC 7 is still the most widely used classification in hypertension management [1].

However, the 2003 ESC/ESH Guidelines as well as the 2003 WHO/ISH Statement on management of hypertension did not share JNC 7's view, since they indicated that the term "prehypertension" could be confusing and might detract attention from investigation of the mechanisms raising BP and diminish the case for tight BP control [1–3]. So, during the ten year period since JNC 7's publication, in the ESC/ESH Guidelines of management arterial hypertension published in 2007, 2009, and even in 2013, no change in classification has been made (Table 2) [4,9,10].

2. Blood pressure goals

In ten years, many conflicting results from observational studies and randomized-controlled trials have affected the BP goals for hypertensive patients with and without compelling indication treatment (Table 3).

In the year 2003, data on target BP corresponding to BP classifications and specific indications are rare, and more evidence was available for DBP than for SBP. With the exception of the subgroup of the HOT trial, in which reduction of DBP values to below 90 mm Hg in non-diabetes was not associated with significant advantage in outcome [16], most of the other studies were related to diabetes, such as: UKPDS [17], ABCD-NT [18], ABCD-HT [19], and MICROHOPE trials [20]. In HOT [16], UKPDS [17], and MICROHOPE trials [20], the DBP values

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between 77 and 82 mm Hg could be achieved and associated with benefit. In addition, the SBP values in these 3 trials could not be lowered below 140 mm Hg. ABCD-NT [18] and ABCD-HT [19], at that time, were the only two trials in diabetes that had achieved SBP values below 140 mm Hg, but the only significant reduction in total mortality was obtained by ABCD-HT [19] in much the same way as reduction in stroke seen in ABCD-NT [18]. On the other hand, in other special conditions, SBP values obtained in the intensive treatment groups of some trials favored outcome benefits, but SBP values below 140 mm Hg were rarely achieved. For example, the average SBPs of 138, 144, and 140 mm Hg were achieved in the PROGRESS trial [21] with previous stroke and TIA patients, the PATS trial [22] with post-stroke patients, and the HOPE trial [23] with high risk CVD patients respectively. In CKD patients, conflicting data was obtained about the benefit of lowering SBP to below 140 mm Hg [24–26]. So, JNC 7 recommendations [1] and the 2003 ESC/ESH guidelines [2] were similar in target BP, except for the case of CKD and initial therapy for high-normal range BP in high and very high risk individuals.

Later, in the year 2007–2008, with the publication of new large randomized trials, ESC/ESH [9] and AHA [12] shared the same view that the target BP below 130/80 should also be used for high risk and very high risk patients. In these studies, a lower BP target in comparison with values in previous major recommendations favored benefits in CVD outcome, such as the CAMELOT trial (BP of 124/76 mm Hg better than 130/77 mm Hg) [27], and the EUROPA trial (128/78 mm Hg rather than 133/80 mm Hg) [28]. Therefore, it was reasonable to consider the target BP of below 130/80 to be more suitable for high risk and very high-risk patients.

Until 2009, continuously updated information led to new changes in treatment strategy. During a long time, pharmacological treatment was recommended for high risk patients with high normal BP range in ESC/ESH guidelines [10], but evidence supporting this view was scant. In most studies, clear-cut benefits of BP-lowering drugs were seen only when initial SBP was higher than 140 mm Hg. In low-to-moderate risk patients, the benefit of BP-lowering therapy was almost consistently seen in individuals with initial SBP ≥ 160 mm Hg (recommended in CHEP Guidelines) [13,15]. In coronary high risk patients, the HOPE [23], CAMELOT [27], EUROPA [28], PEACE [29], ACCESS [30], and PROFESS trials [31] could not prove the persistent benefit when the obtained BP was below 130/80 as well as the advantage of high BP range treatment, except for the EUROPA [28] and CAMELOT trials [27]. Moreover, few trials seem to approve the goal of a BP of <130/80 mm Hg for diabetes patients. In many trials in hypertensive diabetic patients (HOT [16], SHEP [32], UKPDS [17], Syst-Eur [33], ABCD [34], ADVANCE [35], and PROGRESS [21] trials), only the ABCD-NT [18] trial achieved BP below 130/80 mm Hg (average BP value of 128/75 mm Hg); however, the CV outcome benefit was not significant. Recently, a similar finding was seen in the ACCORD trial (2010), which cannot indicate a significant reduction in incidence of major CV events between those whose SBP lowered to an average of 119 mm Hg and those whose SBP remained at an average of 133 mm Hg [36]. In addition, the DBP values between 77 and 82 mm Hg were proved to be safe and beneficial in the HOT [16], UKPDS [17], and MICROHOPE trials [20]. So, in the new ESC/ESH Guidelines in 2013 [4], the BP target for diabetes mellitus patients is recommended to be below 140/85 mm Hg (Class I, Level A).

For the elderly, the HYVET study [37] has been considered the key data for hypertension management. Before this trial (2008), most of the major hypertension guidelines had had the same target BP for all patients, regardless of age, and few studies mentioned the octogenarians. In the HYVET [37], all of these individuals were older than 80 with the initial SBP ≥ 160 mm Hg, the lowering of BP to the average value of 144/78 mm Hg was associated with a significant reduction in all-cause mortality as well as the incidence of stroke, CHF, CV morbidity, and fatal events.

Table 1
JNC 7 classification of BP for adults.

Blood pressure classification	SBP (mm Hg)		DBP (mm Hg)
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Stage 1	140–159	or	90–99
Stage 2	≥160	or	≥100

SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 2
ESC/ESH classification of BP levels.

Blood pressure classification	SBP (mm Hg)	DBP (mm Hg)
Optimal	<120	<80
Normal	120–129	80–84
High normal	130–139	85–89
Grade 1 hypertension (mild)	140–159	90–99
Grade 2 hypertension (moderate)	160–179	100–109
Grade 3 hypertension (severe)	≥180	≥110
Isolated systolic hypertension	≥140	<90

SBP: systolic blood pressure; DBP: diastolic blood pressure.

3. Monotherapy versus combination therapy

In 2002, ALLHAT — the largest hypertension clinical trial ever conducted which contributed major data for JNC 7, indicated that only about one third of the patients achieved the target BP (<140/90 mm Hg) induced by antihypertensive monotherapy [41]. Moreover, the HOT [16], CONVINCE [38], and LIFE trials [39] also had this similar finding. So, JNC 7 [1] recommended initiating antihypertensive treatment in Stage 1 hypertension with monotherapy, and when BP was not well controlled by single drug usage (that is BP > 20 mm Hg above systolic goal and >10 mm Hg above diastolic goal), combination therapy should be initiated. In Stage 2 hypertension as well as in some compelling indications (diabetes mellitus, IHD, CKD, stroke and HF), beginning antihypertensive treatment with drug combinations was also recommended since this therapy was the most popular one in trials related to these high risk patients. Again, ESC/ESH 2003 [4] and BHS 2004 [11] shared somewhat similar views, although their recommendations were not as detailed as JNC 7's [1].

In the later edition of ESC/ESH Guidelines [4,9,10] on hypertension, results suggested initiating monotherapy only in mild BP elevation with low or moderate total CV risk, and beginning combination treatment of two drugs at low doses for Grade 2 and Grade 3 hypertensive individuals or mild BP elevation patients with high or very high risk (target organ damage, diabetes, renal disease, or a history of CVD).

Finally, the similar recommendations of combination antihypertensive treatment have been again reconfirmed in later updated Guidelines of AHA and ACC in 2007 [12] and 2011 [14] as well as in CHEP 2012 and 2013 [15], and in ESC/ESH Guidelines 2009 [10] and 2013 [4] with the important data taken from a meta-analysis of 42 trials. In these trials, the combination of two agents from any different classes of antihypertensive drugs not only induces better BP control than the increase in the dose of current-use agent, but also limits the adverse side effects of high-dose single antihypertensive treatment [40].

3.1. Choice of drugs as monotherapy in hypertensive treatment

Based mainly on the ALLHAT trial [41] as well as the availability and cost of drugs, JNC 7 Guidelines [1], 2003 WHO/ISH Statement