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The 2007 ESH/ESC Guidelines for the management of arterial hypertension

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The Journal of Hypertension has recently published the new ESH/ESC guidelines for the management of arterial hypertension [1].

Overall, the published ISH/WHO, ESH/ESC and ACC/AHA guidelines have similar recommendations, the evidence based on the same trials. However, both the definitions and classification of blood pressure (BP) levels are very different from one another. Thus, the understanding of optimal medical management of hypertension might remain unclear for many physicians, mostly general practitioners, who are increasingly in charge of these patients.

As in the last decade systolic BP was considered as having higher predictive value than diastolic BP [2], physicians did not pay enough attention to phase V (disappearance) of Korotkoff sounds, forgetting that differences such as 120/85 and 120/92 mmHg do not have the same relevance in high-risk patients.

The authors decided not to use the term ‘prehypertension’ coined by the USA Joint National Committee Guidelines (JNC 7) on hypertension published in 2003 [3]. The former argued that in practice this category is a highly differentiated one, with extremes consisting of subjects in no need of any medication (e.g. an elderly individual with a BP of 120/80 mmHg) as well as of those with a very high or high-risk profile (e.g. after stroke or with diabetes) in whom drug treatment is required. For the same reasons, we consider that high-risk patients such as patients with diabetes with optimal BP do not have the same cardiovascular outcome as those with isolated diastolic hypertension.

Scientific knowledge about the relative burden of systolic and diastolic levels of BPs on cardiovascular risk has changed recently reaching a similar predictive value for stroke and coronary mortality, particularly in individuals under 55 years of age [4].

From Table 1 showing definitions and classification of BP in the current ESH/ESC guidelines, it is clear that isolated diastolic hypertension (IDH) should be considered as a specific problem. Nevertheless, no subheading of the current guidelines focuses on management of IDH, although it is already proven that IDH is a marker for future onset of systolic–diastolic hypertension (SDH) [5], with a hazard ratio for risk relation reaching 23.12 ($P < 0.001$) found by Franklin et al. [6] in the Framingham Heart Study.

In terms of preventive medicine, it would be valuable for our daily practice to introduce a specific class for IDH in Table 1 listing definitions and classification of BP aiming at a better management of arterial hypertension (Figs 1 and 2 of the current guidelines). Thus, we would not forget to give instructions for lifestyle changes to patients with IDH and cardiovascular risk factors such as diabetes and renal function impairment. They would certainly benefit from actions against overweight, smoking, alcohol abuse, physical inactivity and/or excess of saturated and total fat intake.

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Reply

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Bonny et al. [1] correctly point out that in the Table 1 of the ESH/ESC guidelines [2] there is no subheading for isolated diastolic hypertension. We agree with them that
this condition can be seen in young patients, although with an overall prevalence much lower than the prevalence of isolated systolic hypertension, which can be the most common and risky hypertension subtype in elderly patients [3]. This, however, cannot lead to the conclusion that in the ESH/ESC guidelines, physicians are not clearly reminded of the need to diagnose hypertension based on a diastolic blood pressure (BP) elevation when systolic BP is within the normal range, and give this condition appropriate treatment. First, the ESH/ESC guidelines repeatedly state that both systolic and diastolic BPs show a graded independent relationship with the incidence of cardiovascular events and in the subheading devoted to systolic versus diastolic and pulse pressure, they recommend classification of hypertension and risk assessment to continue to be based on systolic and diastolic BPs. Second, in Table 1 each BP level is defined by systolic and/or diastolic values. This means that an individual with, for example, a systolic BP less than 140 mmHg but a diastolic BP of 90–99, 100–109 or greater than or equal to 110 mmHg has to be classified as having grade 1, 2 or 3 hypertension, respectively.

Finally, in Figs. 1 and 2 (as well as in the text) treatment recommendations are given for elevations in systolic and/or diastolic BP. This means that, the lifestyle changes and, if BP remains uncontrolled, the antihypertensive drugs recommended for individuals at low or moderate added risk apply also to the condition in which systolic BP is normal whereas diastolic BP is modestly or more clearly elevated such as when there is isolated diastolic hypertension. Similarly, the lifestyle changes and drug treatment recommended for diabetic patients with a BP in the high normal range involve individuals having a diastolic BP of 85–99 mmHg with a systolic pressure values in the normal or even optimal range.

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Dipping in type II diabetes: autonomic and diuretics

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The report of Astrup et al. [1] on mortality predictors in type II diabetes is extremely informative, despite the small cohort size. We were concerned by two issues raised in the discussion of the article. Firstly, Astrup et al. cite the work of Uzu and Kimura [2] as evidence for the feasibility of chronotherapy. The therapy used effectively by Uzu and Kimura to convert nondippers to dippers may, however, be considered chronotherapy only in the sense that it is a chronologically abandoned treatment. Uzu et al. [3] applied sodium restriction or diuretic treatment [4] to patients with essential hypertension, both resulting in enhanced blood pressure dipping. Diuretics were administered at 0700h. Thus, chronotherapy was not involved.

Secondly, while emphasizing the role of sleep apnea, Astrup et al. [1] claim that ‘there is no evidence that cardiac autonomic neuropathy (CAN) leads to the non-dipping phenomenon’ [1]. We disagree. One of the more disabling features of CAN namely, orthostatic hypotension, is closely associated with nondipping. This was surely noticed by the authors in their clinical practice. Thus, milder forms of the neuropathy ought to correlate as well. Indeed, there are several reports linking diabetic neuropathy with blood pressure non-dipping [4,5]. In addition, it has been noted that a lesser blood pressure response to sleep, even to a short afternoon nap, maybe a harbinger of diabetic autonomic neuropathy [6].

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In the comment by Iddo Z. Ben-Dov and Michael Bursztyn, they argue that the therapy applied by Uzu...
et al. is not chronotherapy; however, the two important papers by Uzu and Kimura [1] and Uzu et al. [2], prove that it is possible for some nondippers to obtain normal circadian blood pressure (BP) rhythm by applying a treatment (or restriction) that has influence on the BP rhythm round the clock. Thus, treatment in patients with nondipping should apply sodium restriction, diuretics, or some other drug with the same influence on the nondipping phenomenon. Hermida and Smolensky [3] provide an overview of different regimes of chronotherapy.

Furthermore, Ben-Dov and Bursztyn disagree that the causality between cardiac autonomic neuropathy and nondipping is not yet clear. We are aware of the correlation between autonomic neuropathy and nondipping, but this does not prove the causality between the two symptoms. Some patients have cardiac autonomic neuropathy without being nondippers. Most likely the pathophysiological pathway leading to these two clinical symptoms is strongly connected, and thus the association between these two parameters is evident in several studies.

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Central vs. peripheral leptin excess in the pathogenesis of obesity-associated hypertension
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I have read with great interest the article by Tümer et al. [1] on the role of leptin in obesity-associated hypertension. Previous studies have demonstrated that chronic leptin administration or transgenic overexpression increases blood pressure in experimental animals [2,3]. As plasma leptin concentration is markedly increased in obese individuals, it is suggested that obesity-associated hyperleptinemia contributes to the development of hypertension [4]. The direct evidence of this link, however, was lacking because no attempts have been made to examine if switching off leptin signaling reduces blood pressure (BP) in obese animals. Tümer et al. [1] used the recently developed leptin antagonist to address this issue. The authors examined the effect of this antagonist administered intracerebroventricularly on blood pressure (BP) in two experimental models: chronic hypothalamic overexpression of leptin by recombinant adenoviral vector (rAAV-leptin) in lean rats, and high-fat diet-induced obesity. It was observed that rAAV-leptin vector induced a transient decrease in food intake, which waned over time, suggesting the development of leptin-induced resistance to the anorectic effect of this hormone. The body weight and adiposity, however, were permanently lower in the rAAV-treated group than in control rats. BP was increased in the leptin-overexpressing group despite reduced adiposity. Leptin antagonist infused for 2 weeks starting from the 155th day after the injection of rAAV-leptin vector reduced BP to normal level. In the high-fat obesity model, leptin antagonist further increased food intake and weight gain over the level observed in the vehicle-infused obese group, indicating that, despite obesity-induced leptin resistance, endogenous leptin still had some reducing effect on food intake and body weight. Interestingly, leptin antagonist failed to reduce blood pressure in obese rats [1]. The authors conclude that although artificially induced central excess of leptin increases BP in lean animals, endogenous leptin is not involved in obesity-associated hypertension. This study is very significant because it is the first one that attempted to examine what happens with BP in obese animals if leptin signaling is switched off. Although the conclusion that leptin is not a key factor in obesity-associated hypertension may be plausible, the alternative explanation should also be considered.

Initial studies suggested that prohypertensive effect of leptin is mediated solely by stimulation of the sympathetic nervous system at the central level [5,6]. Many potentially prohypertensive peripheral effects of leptin, however, have also been described. Leptin stimulates reactive oxygen species (ROS) formation both in vitro [7] and in vivo [8], and ROS exert vasoconstriction and renal Na⁺ retention in various models of hypertension [9]. Moreover, leptin stimulates synthesis and secretion of vasoconstrictor endothelin-1 by endothelial cells [10], and promotes hypertrophy of vascular smooth muscle cells thus increasing peripheral vascular resistance [11]. Interestingly, leptin has been recently demonstrated to transactivate the epidermal growth factor receptor (EGFR) in vascular smooth muscle cells [12]. EGFR is transactivated by various vasoconstrictors, and increased EGFR signaling is observed in many models of hypertension [13,14]. Leptin activates EGFR also in the kidney, which may contribute to abnormal renal Na⁺ handling [15].

The results presented by Tümer et al. [1] may indicate that these peripheral effects of leptin are more important in mediating obesity-associated hypertension than
stimulation of the sympathetic nervous system (SNS) at a central level. Indeed, leptin antagonist reduced the SNS activity in obese rats as evidenced by decreased heart rate and tyrosine hydroxylase expression in the cervical ganglia, but failed to reduce BP. It should be noted that plasma leptin was two-fold higher in obese rats than in chow-fed rats [1], and centrally administered leptin antagonist neither reduced plasma leptin nor could block the peripheral effects of this hormone. In contrast, hypothalamic overexpression of leptin caused a marked decrease in plasma leptin concentration due to depletion of adipose tissue [1]. Thus, the central sympathoexcitatory effect of locally overexpressed leptin is the only mechanism of BP elevation in the rAAV-leptin model, and therefore, centrally administered leptin antagonist effectively reduces BP. Further studies in which peripheral leptin signaling was switched off by pharmacological or genetic approaches are required to verify whether this explanation of results presented by Tümer et al. [1] is correct.

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Can we treat patients according to the latest hypertension trials?

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This paper is about an imaginary physician and a hypertensive patient. The treatment is guided by the latest hypertension trial each year wherein the physician tries to inform the patient about the merits of the treatments. Patients should be treated using the latest medical developments and there is no doubt that we should treat them with the support of at least one recent clinical study. If, however, we were to follow hypertension trials promptly every year and adapt treatment methodologies and follow the latest data, we would confuse ourselves and scare away patients.

Suppose we have a physician, Dr Jones, who enthusiastically studies a large clinical hypertension trial each year and applies this to his practice, which he started after graduating in 2000. His first hypertensive patient, Mr Smith, a 65-year-old white Caucasian male, would start with diltiazem in 2000 [1], switch to perindopril the next year [2] and change to chlorothalidone in 2002 [3]. In 2003, Mr Smith needs to go back to an angiotensin-converting enzyme (ACE) inhibitor, and if Dr Jones explains to him that antihypertensive therapy based upon ACE inhibitors, compared with diuretics, appeared to provide a superior benefit in some cardiovascular outcomes in elderly men [4], Mr Smith would be very excited too.

In 2004, Dr Jones is thrilled to tell Mr Smith that he is really getting a good hand in treating hypertensive patients. He learned that the decisions on which antihypertensive agents to be used will have to be tailored to the needs of the patients with careful consideration of medical factors. Therefore, he tells Mr Smith that the best way to determine the optimal treatment in his case is by tossing a coin to decide whether to use a diuretic, a calcium channel blocker or an ACE inhibitor, as there seems to be an equal outcome between their use [5,6]. The diuretics won, but in 2005, Mr Smith really had to go on amlodipine, as this may lead to a lower rate of cardiovascular disease and mortality [7]. Fed up with all these changes and new trial data, Mr Smith refuses to listen to a new trial in 2006, so Dr Jones decides to discuss the older trials again. This conversation may go as follows: ‘Mr. Smith, I am glad you are such an understanding patient, because I have to change your medication again. After reviewing the trials, I discovered several interesting limitations of these studies. Although subset analysis suggested that diltiazem provided significantly better protection against stroke, this benefit may
have been due to a chance, given the number of statistical comparisons performed in this study. An alternate explanation is that the lesser protection from stroke resulted from the 3 mmHg higher systolic pressure in those on conventional therapy [2]. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [3] and Second Australian National Blood Pressure Study (ANBP-2) [4] used different drugs and vastly different definitions of primary and secondary outcomes [8] and the percentages of patients with diabetes, smokers, and patients with coronary heart disease or cerebrovascular disease in ANBP2 were lower [4]. These characteristics could also have an effect on outcomes. But there is more Mr. Smith: in the ALLHAT study, the wrong add-on drugs were provided and demographics should have favored diuretics, but the blood pressure differences accounted for differences in outcome [3], so I am not so sure what to think about that. The ANBP-2, however, favored an ACE inhibitor, but the study was not blinded [4]. On top of that, the B-blocker used in the Anglo-Scandinavian Cardiac Outcomes Trial was inappropriately dosed [7]; atenolol is not a once-a-day drug, as you probably know. But do you believe that in almost all the trials it was frequently necessary to prescribe a second and even a third medication in order to control the blood pressure [8]? You know what, Mr. Smith, personally, I think that the design of the trials should be different, because, in my opinion, they should compare a combination of three medications with another combination of three others, as monotherapy and even two antihypertensive medications are often inadequate in hypertension treatment. Therefore, I am convinced that you may be better off with three or maybe even four classes of antihypertensive medications simultaneously."

‘Please forget everything I said about the trials the past years,’ Dr Jones told Mr. Smith in 2007 after reading a recent paper. ‘Patients with hypertension participating in trials may differ in many aspects from patients treated in general practices. A Dutch group evaluated 21 trials and found out that trial participants were usually not recruited from general practices, that the patients were younger, at lower risk of getting cardiovascular disease, and often had less history of cardiovascular disease or comorbidity [9]. Moreover, the results of randomized clinical trials might not apply in a straightforward way to individual patients, even those within the trial! Although randomization theoretically ensures the comparability of treatment groups overall, there remain important differences between individuals in each treatment group that can dramatically affect the likelihood of benefiting from or being harmed by a therapy [10]. Averaging effects across such differing patients can give misleading results to physicians who care for individual, not average, patients.’

Mr. Smith, extremely upset and angry, decided to find a less confused physician who can treat a simple disease like hypertension. Accompanying him to the doorway Dr Jones managed to say, ‘You know, Mr. Smith, to be honest, I always had a funny feeling about these trials, but maybe I can tell you more next year.’

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