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Review Paper

Diagnostic Thresholds for Ambulatory Blood Pressure Moving Lower: A Review Based on a Meta-Analysis—Clinical Implications

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Upper limits of normal ambulatory blood pressure (ABP) have been a matter of debate in recent years. Current diagnostic thresholds for ABP rely mainly on statistical parameters derived from reference populations. Recent findings from the International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome (IDACO) provide outcome-driven thresholds for ABP. Rounded systolic/diastolic thresholds for optimal ABP were found to be 115/75 mm Hg for 24 hours, 120/80 mm Hg for daytime, and 100/65 mm Hg for nighttime. The corresponding rounded thresholds for normal ABP were 125/75 mm Hg, 130/85 mm Hg, and 110/70 mm Hg, respectively, and those for ambulatory hypertension were 130/80 mm Hg, 140/85 mm Hg, and 120/70 mm Hg. However, in clinical practice, any diagnostic threshold for blood pressure needs to be assessed in the context of the patient's overall risk profile. The IDACO database is therefore being updated with additional population cohorts to enable the construction of multifactorial risk score charts, which also include ABP. J Clin Hypertens (Greenwich). *2008;10:377–381.* ©*2008 Le Jacq*

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The relation between cardiovascular risk and blood pressure, irrespective of the technique of measurement, is continuous.[1] However, clinicians need a diagnostic reference frame to interpret blood pressure values and to classify patients. Some guidelines for the diagnosis and management of hypertension reflect consensus about the thresholds for optimal (<120/80 mm Hg) and normal (<130/85 mm Hg) blood pressure and hypertension (>140/90 mm Hg) on conventional office measurement.[2–4] However, ambulatory blood pressure monitoring is increasingly being used in clinical practice for the diagnosis and management of hypertension.[2] Over the past 10 years, experts have proposed preliminary criteria for normality of the ambulatory blood pressure, based on its distribution in normal reference populations.

STATISTICALLY DETERMINED THRESHOLDS IN PATIENTS WITH UNTREATED HYPERTENSION

Several investigators have proposed diagnostic thresholds based on the distribution of the ambulatory blood pressure in normotensive subjects and in patients with untreated hypertension who had initially been classified on the basis of their

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conventional blood pressure.[5–10] Among 4577 persons with normotension on conventional sphygmomanometry enrolled in the International Database on Ambulatory Blood Pressure Monitoring, the systolic/diastolic 95th percentile limits were 133/82 mm Hg, 140/88 mm Hg, and 125/76 mm Hg for the 24-hour, daytime, and nighttime blood pressure values, respectively.[5]

Other investigators have computed the regression line between the ambulatory and conventional blood pressure levels of individual patients and determined the ambulatory blood pressure level corresponding to a conventional blood pressure of 140 mm Hg systolic and 90 mm Hg diastolic.[9,11–14] Plots relating the ambulatory blood pressure to conventional blood pressure values show a wide scatter of data points around the regression line. Consequently, with the regression method, many patients who are normotensive based on their conventional blood pressure are classified as hypertensive based on their ambulatory blood pressure. The 95% prediction interval for individual values around the regression line accounts, to some extent, for this scatter. The regression method also assumes that the independent variable, that is the conventional blood pressure, is fixed, whereas in reality it is characterized by high variability.

The percentile method requires that the same percentage of patients be classified as hypertensive, irrespective of whether the diagnosis relies on conventional or ambulatory blood pressure measurement. The percentile approach does not account for the discrepancy between the 2 types of measurement, as observed in patients with white-coat hypertension (elevated conventional blood pressure but normal ambulatory blood pressure) or masked hypertension (normal conventional blood pressure but elevated ambulatory blood pressure).

The limitations of these statistical approaches highlight the necessity to validate the diagnostic thresholds of ambulatory blood pressure in terms of target organ damage or, even better, in relation to "hard" cardiovascular outcomes.

THRESHOLDS IN INDIVIDUAL OUTCOME STUDIES

Some studies have validated preliminary thresholds for ambulatory blood pressure based on its distribution or on the correlation with signs of left ventricular hypertrophy.[15–17] In 1994, Verdecchia and coworkers[18] published the first prospective study relating the incidence of cardiovascular complications to the level of the ambulatory blood pressure. They analyzed the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) cohort of hypertensive patients. They showed that the incidence of cardiovascular events was the same in patients with white-coat hypertension and in normotensive persons when the diagnostic threshold for systolic/diastolic hypertension on ambulatory measurement was set to 131/86 mm Hg in women and to 136/87 mm Hg in men.[18] In a further analysis of the same cohort,[19] the patients with white-coat hypertension were subdivided into those with an average daytime blood pressure of <130/80 mm Hg as opposed to those whose daytime blood pressure was between 130/80 and 131/86 mm Hg in women or between 130/80 and 136/87 mm Hg in men. The differences in event-free survival rates between the normotensive group and the group with white-coat hypertension, as defined more strictly (<130/80 mm Hg), were not statistically significant. In contrast, the rate of cardiovascular complications was significantly higher in the white-coat hypertensive patients as defined less restrictively (up to 131/86 mm Hg in women and 136/87 mm Hg in men), compared with the normotensive patients. On the basis of these results, Verdecchia[20] suggested in 2000 that a daytime blood pressure of 130 mm Hg systolic and 80 mm Hg diastolic might be defined as the optimal thresholds to identify white-coat hypertensive patients at low cardiovascular risk, not dissimilar from persons with sustained normotension.

In 1998, Japanese investigators published the first population-based outcome study proposing reference values for ambulatory blood pressure based on the risk of death.[21] Among 1542 inhabitants from the city of Ohasama, Japan, the optimal 24-hour blood pressure resulting in the lowest all-cause mortality ranged from 120 to 133 mm Hg systolic and from 65 to 78 mm Hg diastolic. Over a mean follow-up of 6.2 years, the levels of the 24-hour blood pressure above and below these thresholds were associated with increased risks of cardiovascular and noncardiovascular mortality, respectively.[21]

THRESHOLDS IN A META-ANALYSIS OF POPULATION STUDIES

Collaborative meta-analyses of individual patient data constitute a powerful research tool over and beyond the prognostic information generated by single-cohort studies.[1,22] The International Database on Ambulatory Blood Pressure Monitoring constructed in 1993 and 1994[5] lacked a prospective dimension. We therefore constructed a new International Database with the objective to clarify the relation between the incidence of cardiovascular

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complications and various statistics derived from the ambulatory blood pressure as recorded at baseline. One of the prespecified objectives[23] was to define outcome-based diagnostic thresholds for the ambulatory blood pressure. The acronym of the new database is IDACO, which stands for International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome.[23]

Studies eligible for inclusion in IDACO had to include a random population sample with longitudinal follow-up of fatal and nonfatal cardiovascular outcomes.[23] In January 2007, the IDACO database included 7609 subjects: 2311 residents from Copenhagen, Denmark[24]; 2542 subjects recruited from Noorderkempen, Belgium[25]; 1535 inhabitants of Ohasama, Japan[26]; and 1221 men from Uppsala, Sweden.[27] Of the 7609 participants, we excluded 1927 because their conventional or nighttime blood pressures had not been measured or because their daytime or nighttime blood pressures were the averages of <10 or <5 readings, respectively. Thus, the number of participants included in the analyses totaled 5682.[28]

Table I lists the baseline characteristics of the cohort. Of the participants, 618 (10.9%) had white-coat hypertension (conventional blood pressure ≥140/90 mm Hg and daytime blood pressure <135/85 mm Hg) and 866 (15.2%) had masked hypertension (<140/90 and ≥135/85 mm Hg). Over a median follow-up of 9.7 years (5th to 95th percentile interval, 2.3–14.1 years), 814 cardiovascular end points occurred, including 377 strokes and 435 cardiac events.[28]

Table I. Baseline Characteristics of the IDACO Cohort

Characteristic	All
No. of Participants	5682
Women, No. (%)	2461 (43.3)
Age, y	59.0 (12.5)
Body mass index, kg/m^2	25.4 (3.9)
Blood pressure, mm Hg	
Conventional systolic	133.3 (19.8)
Conventional diastolic	79.9 (11.4)
24-Hour systolic	126.2 (14.1)
24-Hour diastolic	73.7 (8.2)
Daytime[a] systolic	133.1 (15.0)
Daytime[a] diastolic	78.7 (9.1)
Nighttime[b] systolic	114.0 (15.4)
Nighttime[b] diastolic	64.7 (9.0)
Serum cholesterol, mg/dL[c]	222.4 (44,1)
Diabetes mellitus, No. (%)	453 (8.0)
Cardiovascular disease, No. (%)	510 (9.0)
Antihypertensive treatment, No. (%)	1338 (23.5)

Abbreviation: IDACO, International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome. Data are mean (SD) unless otherwise indicated. [a]Daytime ranged from 10 AM to 8 PM in Europeans and from 8 AM to 6 PM in Japanese participants. [b]Nighttime intervals ranged from midnight to 6 AM in Europeans and from 10 PM to 4 AM in Japanese participants. [c]To convert serum total cholesterol levels to mmol/L, multiply by 0.02586.

One key issue in the determination of outcome-based thresholds is the notion of which level of risk is normal or acceptable. We chose to conform with the general consensus in current guidelines[2–4] and determined levels of the ambulatory blood pressure yielding risks equivalent to those associated with optimal (<120/80 mm Hg) and normal (<130/85 mm Hg) blood pressure and hypertension (>140/90 mm Hg) on conventional measurement. We did not designate patients with high-normal blood pressure as prehypertensive, as proposed by the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).[29] The steps in the statistical analysis were as follows. First, we determined the 10-year incidence rates of cardiovascular end points associated with optimal or normal blood pressure or hypertension on conventional blood pressure measurement. Second, the ambulatory blood pressure levels, which were associated with similar 10-year risks as the conventional blood pressure thresholds were calculated. Finally, we rounded the so-obtained thresholds to zero or five to derive more easily recallable outcome-driven blood pressure thresholds.[28]

After rounding, approximate thresholds for optimal ambulatory blood pressure amounted to 115/75 mm Hg for the whole day, 120/80 mm Hg for daytime, and 100/65 mm Hg for nighttime. Rounded thresholds for normal ambulatory blood pressure were 125/75 mm Hg, 130/85 mm Hg, and 110/70 mm Hg, respectively, and those for ambulatory hypertension were 130/80 mm Hg, 140/85 mm Hg, and 120/70 mm Hg.[28] In the outcome analyses, we only adjusted for cohort. We performed sensitivity analyses, from which we excluded one cohort at a time or patients receiving antihypertensive drug treatment. This produced consistent results with little change in the proposed ambulatory cutoffs.[28]

The IDACO-derived diagnostic thresholds for ambulatory blood pressure measurement must be interpreted within the context of some potential limitations. First, the proposed threshold values do not

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Table II. Systolic and Diastolic Cutoffs for Normality in IDACO and According to Published Hypertension Guidelines

	IDACO Database, 2007[28]	ESH Guidelines, 2005[31]	AHA Recommendations, 2005[30]	ESH/ESC Guidelines, 2007[3]
Optimal blood pressure				
24-hour	<115/75	No threshold	<125/75	NA
Daytime	<120/80	<130/80	<130/80	NA
Nighttime	<100/65	<115/65	<115/65	NA
Normal blood pressure				
24-hour	<125/75	No threshold	<130/80	NA
Daytime	<130/85	<135/85	<135/85	NA
Nighttime	<110/70	<120/70	<120/70	NA
Hypertension				
24-hour	≥130/80	No threshold	>135/85	≥125–130/80
Daytime	≥140/85	>140/90	>140/90	≥130–135/85
Nighttime	≥120/70	>125/75	>125/75	≥120/70

Abbreviations: AHA, American Heart Association; ESC, European Society of Cardiology; ESH, European Society of Hypertension; IDACO, International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome; NA, not available. All values are mm Hg.

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account for sex, age, or other cardiovascular risk factors. However, the boundaries currently in use for the definition of normotension and hypertension on conventional blood pressure measurements are also uniformly applicable to women and men and across all ages. Second, the analyses rested only on 4 population-based cohorts and might therefore not be representative for non-European or non-Japanese patients. In addition, the study population predominantly included older adults. Of the participants, only 2.1% and 5.9% were younger than 30 or 40 years, respectively.

Table II summarizes the systolic/diastolic cutoffs for normality in the current guidelines for the management of hypertension and the thresholds proposed from the analyses of the IDACO database. Compared with the guidelines from the American Heart Association and from the European Society of Hypertension published in 2005,[30,31] the suggested thresholds from the IDACO database are lower or identical for optimal and normal blood pressure as well as for hypertension. The guidelines issued by the European Society of Hypertension and the European Society of Cardiology published in 2007[3] do not propose thresholds for optimal or normal blood pressure.

CLINICAL IMPLICATIONS AND PERSPECTIVES

How can the clinician apply the currently proposed ambulatory thresholds? First, it is important to realize that the relation between cardiovascular outcome and blood pressure is continuous. In other words, there is no critical level above which the risk suddenly rises.[1] Thus, thresholds only serve the need of clinicians to use cutoffs for the diagnosis and management of hypertension. Second, current guidelines[3,29] for the management of hypertension move away from the point of view of blood pressure as an isolated risk factor and increasingly introduce the concept of the management of global cardiovascular risk in individual patients. Thus, a given blood pressure needs to be assessed within the context of the overall risk profile of an individual patient, the level of target organ damage, and the presence of associated conditions.[24,32] The calculation of the absolute cardiovascular risk is key to the stratification of risk in individual patients.[24,32,33] As described elsewhere,[23] and as already partially implemented,[34] the IDACO database is therefore being updated with additional population cohorts to enable the construction of multifactorial risk score charts, which account for the ambulatory blood pressure in conjunction with other risk factors, such as sex, age, smoking status, and the serum level of total cholesterol.

Furthermore, when making decisions based on ambulatory blood pressure, the number of readings must be assessed to ensure that the recording actually represents 24 hours. In addition, when evaluating nighttime blood pressure, it is important to obtain information on quality and duration of sleep.

Finally, we would strongly favor the implementation of a randomized intervention trial to test that treatment in keeping with the proposed thresholds of ambulatory blood pressure is successful in delaying the progression of target organ damage and in improving the prevention of cardiovascular events.

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