

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Circulation 2007;115;2145-2152; originally published online Apr 9, 2007;

DOI: 10.1161/CIRCULATIONAHA.106.662254

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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Diagnostic Thresholds for Ambulatory Blood Pressure Monitoring Based on 10-Year Cardiovascular Risk

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Background—Current diagnostic thresholds for ambulatory blood pressure (ABP) mainly rely on statistical parameters derived from reference populations. We determined an outcome-driven reference frame for ABP measurement.

Methods and Results—We performed 24-hour ABP monitoring in 5682 participants (mean age 59.0 years; 43.3% women) enrolled in prospective population studies in Copenhagen, Denmark; Noorderkempen, Belgium; Ohasama, Japan; and Uppsala, Sweden. In multivariate analyses, we determined ABP thresholds, which yielded 10-year cardiovascular risks similar to those associated with optimal (120/80 mm Hg), normal (130/85 mm Hg), and high (140/90 mm Hg) blood pressure on office measurement. Over 9.7 years (median), 814 cardiovascular end points occurred, including 377 strokes and 435 cardiac events. Systolic/diastolic thresholds for optimal ABP were 116.8/74.2 mm Hg for 24 hours, 121.6/78.9 mm Hg for daytime, and 100.9/65.3 mm Hg for nighttime. Corresponding thresholds for normal ABP were 123.9/76.8, 129.9/82.6, and 110.2/68.1 mm Hg, respectively, and those for ambulatory hypertension were 131.0/79.4, 138.2/86.4, and 119.5/70.8 mm Hg. After rounding, approximate thresholds for optimal ABP amounted to 115/75 mm Hg for 24 hours, 120/80 mm Hg for daytime, and 100/65 mm Hg for nighttime. Rounded thresholds for normal ABP were 125/75, 130/85, and 110/70 mm Hg, respectively, and those for ambulatory hypertension were 130/80, 140/85, and 120/70 mm Hg.

Conclusions—Population-based outcome-driven thresholds for optimal and normal ABP are lower than those currently proposed by hypertension guidelines. (*Circulation*. 2007;115:2145-2152.)

Key Words: blood pressure monitoring, ambulatory ■ blood pressure ■ hypertension ■ cardiovascular diseases ■ epidemiology

In middle-aged and older subjects, hypertension is the predominant cardiovascular risk indicator. Blood pressure measurement is the basis for the diagnosis and treatment of hypertension. Conventional blood pressure measurement by auscultation of the Korotkoff sounds is fraught with potential sources of error, which may arise in the patients, the observer, the sphygmomanometer, or the overall application of the technique.¹ Ambulatory monitoring allows registration of the blood pressure throughout the entire day in subjects engaged in their usual activities. Ambulatory blood pressure recordings have high reproducibility, are not subject to digit preference, and

avoid the transient rise of a patient's blood pressure in response to a medical environment, the so-called white-coat effect.¹

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Although blood pressure is continuously distributed, clinicians need a diagnostic reference frame to interpret ambulatory blood pressure values and to classify patients. Current guidelines¹⁻³ propose operational thresholds for the ambulatory blood pressure, but these limits are not outcome driven, relying largely on the distribution of the ambulatory blood

Received August 31, 2006; accepted February 16, 2007.

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The online-only Data Supplement, consisting of a list of centers, investigators, and database coordinators, is available with this article at <http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.106.662254/DC1>.

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/CIRCULATIONAHA.106.662254

pressure in normotensive reference populations^{4,5} or on the regression of ambulatory on conventional blood pressure.⁵ We therefore constructed an international population-based database with the objective to determine diagnostic thresholds for ambulatory blood pressure monitoring in terms of cardiovascular outcome.

Methods

Study Participants

We constructed the International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO). Eligible studies had to include a random population sample with longitudinal follow-up of fatal and nonfatal cardiovascular outcomes. An electronic search of the English literature, using as search terms "ambulatory blood pressure monitoring" and "population," identified 9 studies.^{4,6-13} Five^{8-11,13} could not be included because at the time of writing of this article, follow-up was still ongoing^{8,9,11,13} or because follow-up did not include nonfatal events.¹⁰

For the present analysis, we considered 2311 residents from Copenhagen, Denmark⁷; 2542 subjects recruited from Noorderkempen, Belgium⁴; 1535 inhabitants of Ohasama, Japan¹²; and 1221 men from Uppsala, Sweden.⁶ Thus, on April 30, 2006, the number of subjects available for analysis totaled 7609. All studies contributing to the IDACO database received ethical approval and have been described in detail in peer-reviewed publications.^{4,6,7,12} All participants gave informed written consent. Of the 7609 subjects, we excluded 1927 because their conventional (n=220) or nighttime (n=1618) blood pressures had not been measured or because their daytime (n=22) or nighttime (n=67) blood pressures were the averages of fewer than 10 or 5 readings, respectively. Thus, the number of subjects included in the present analyses totaled 5682.

Conventional and Ambulatory Blood Pressure Measurement

Experienced observers measured the conventional blood pressure with standard mercury sphygmomanometers^{4,6,7} or validated¹⁴ auscultatory devices (USM-700F, UEDA Electronic Works, Tokyo, Japan),¹² using the appropriate cuff size, after the subjects had rested for at least 2 minutes in the sitting^{4,7,12} or supine⁶ position. The conventional blood pressure was the average of 2 consecutive readings obtained either at the subject's home⁴ or at an examination center.^{6,7,12} We used the thresholds proposed by the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI),¹⁵ the European Society of Cardiology,³ and the European Society of Hypertension³ to classify participants according to their conventional blood pressure. Optimal was a blood pressure level lower than 120 mm Hg systolic and 80 mm Hg diastolic. Normal blood pressure ranged from 120 to 129 mm Hg systolic and from 80 to 84 mm Hg diastolic. Hypertension was a conventional blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic, irrespective of treatment status.

We programmed portable blood pressure monitors to obtain readings either at 20-minute⁶ or 30-minute¹² intervals throughout the day, or at intervals varying from 15 minutes (7 AM to 11 PM) to 30 minutes (11 PM to 7 AM)⁷ or from 20 minutes (8 AM to 10 PM) to 45 minutes (10 PM to 8 AM).⁴ The devices implemented an auscultatory algorithm (Accutracker II, Suntech Medical Instruments Inc, Morrisville, NC) in Uppsala⁶ or an oscillometric technique (SpaceLabs 90202 and 90207, SpaceLabs Inc, Redmond, Wash) in Noorderkempen.⁴ The Takeda TM-2421 recorders (A&D, Tokyo, Japan) and the ABPM-630 devices (Nippon Colin, Komaki, Japan¹⁶), used in Copenhagen⁷ and Ohasama,¹² respectively, implemented both techniques, but we only analyzed the oscillometric readings.

The same SAS macro processed all ambulatory recordings. Mean 24-hour, daytime, and nighttime blood pressures were weighted by the time interval between consecutive readings. While accounting for

the daily pattern of the activities of study participants, we defined daytime as the interval ranging from 10 AM to 8 PM in Europeans^{4,6,7} and from 8 AM to 6 PM in Japanese.¹² The corresponding nighttime intervals ranged from midnight to 6 AM^{4,6,7} and from 10 PM to 4 AM,¹² respectively. These fixed clock-time intervals eliminate the transition periods in the morning and evening, during which blood pressure changes rapidly, and result in daytime and nighttime blood pressure levels that are within 1 to 2 mm Hg of the awake and asleep levels.^{9,17}

Other Measurements

In all cohorts, a questionnaire was used to obtain detailed information on each subject's medical history, intake of medications, and smoking and drinking habits. We defined smoking and drinking as the current use of tobacco and alcohol. Body mass index was body weight in kilograms divided by height in meters squared. Previous cardiovascular disease included cardiac and cerebrovascular disorders and peripheral vascular disease. Serum total cholesterol and blood glucose were determined by automated enzymatic methods on venous blood samples. Diabetes mellitus was a self-reported diagnosis, a fasting or random blood glucose level of at least 7.0 or 11.1 mmol/L (126 or 200 mg/dL),¹⁸ respectively, or the use of antidiabetic drugs.

Ascertainment of Events

We ascertained vital status and incidence of fatal and nonfatal diseases from the appropriate sources in each country, as described in detail in previous publications.^{4,6,7,12,19} Fatal and nonfatal stroke did not include transient ischemic attacks. Coronary events encompassed death due to ischemic heart disease, sudden death, nonfatal myocardial infarction, and surgical and percutaneous coronary revascularization. Cardiac events comprised coronary end points and fatal and nonfatal heart failure. In the Danish and Swedish cohorts, the diagnosis of heart failure required hospitalization. In the Japanese¹² and Belgian¹⁹ cohorts, heart failure was either a clinical diagnosis or the diagnosis on the death certificate, but all cases were validated against hospital records or the records held by general practitioners. The composite cardiovascular end point included all aforementioned end points plus cardiovascular mortality. In all outcome analyses, we only considered the first event within each category.

Statistical Methods

For database management and statistical analysis, we used SAS software, version 9.1 (SAS Institute, Cary, NC). We compared means and proportions by the large-sample *z* test or ANOVA and by the χ^2 test, respectively. To explore the plausibility of the Cox model, we first plotted incidence rates by fifths of the blood pressure distributions, while standardizing by the direct method for cohort, sex, and age (<40, 40 to 60, and \geq 60 years). In Cox regression, we also checked the proportional hazards assumption by the Kolmogorov-type supremum test. In line with large cohort studies,²⁰ we included blood pressure as a continuous linear term in the Cox regression model, but we also tested whether the addition of a quadratic term of blood pressure improved the fit. We calculated hazard ratios, while adjusting for cohort, sex, age, body mass index, smoking and drinking, history of cardiovascular disease, diabetes mellitus, treatment with antihypertensive drugs, and serum total cholesterol. We adjusted for cohort by introducing 3 design variables in the Cox models.

We obtained diagnostic thresholds for ambulatory blood pressure monitoring in 5 steps. First, we computed the 10-year incidence rates of cardiovascular end points associated with optimal or normal blood pressure or hypertension on conventional blood pressure measurement. Second, we computed the 10-year incidence rates of cardiovascular end points associated with ambulatory blood pressure levels ranging from the 5th to the 95th percentiles, using intervals of 0.1 mm Hg. In a third step, we selected the ambulatory blood pressure levels that were associated with similar 10-year risks as the conventional blood pressure thresholds. Next, we calculated the

TABLE 1. Baseline Characteristics by Cohort

Characteristic	Copenhagen (n=2137)	Noorderkempen (n=1131)	Ohasama (n=1317)	Uppsala (n=1097)	All (n=5682)
Women, n (%)	1024 (47.9)	573 (50.7)	864 (65.6)	0 (0.0)	2461 (43.3)
Age, y	56.4 (10.3)	49.0 (14.6)	61.8 (9.9)	71.0 (0.6)	59.0 (12.5)
Range	41.0–72.8	13.4–87.7	40.1–93.1	69.4–74.1	13.4–93.1
Body mass index, kg/m ²	26.0 (4.1)	25.8 (4.2)	23.5 (3.0)	26.3 (3.4)	25.4 (3.9)
Weight, kg	74.9 (14.1)	72.2 (13.4)	54.2 (9.0)	80.3 (11.6)	70.6 (15.6)
Height, cm	169.5 (9.0)	167.0 (9.4)	151.7 (8.6)	174.8 (5.9)	165.9 (11.8)
Conventional blood pressure, mm Hg					
Systolic	131.2 (19.2)	126.7 (17.8)	131.2 (18.5)	146.7 (18.5)	133.3 (19.8)
Diastolic	83.3 (10.7)	76.7 (10.6)	74.1 (11.4)	83.7 (9.4)	79.9 (11.4)
24-Hour blood pressure, mm Hg					
Systolic	128.6 (12.8)	118.8 (11.1)	123.1 (13.2)	132.9 (15.6)	126.2 (14.0)
Diastolic	75.1 (8.6)	71.3 (7.4)	71.9 (7.8)	75.1 (7.7)	73.6 (8.2)
Daytime blood pressure, mm Hg					
Systolic	136.4 (13.6)	125.0 (11.7)	128.9 (14.3)	140.2 (16.2)	133.1 (15.0)
Diastolic	80.5 (9.2)	77.1 (8.2)	76.1 (8.7)	79.8 (8.7)	78.7 (9.0)
Nighttime blood pressure, mm Hg					
Systolic	115.8 (14.1)	108.5 (12.2)	111.6 (14.7)	119.3 (18.6)	114.0 (15.3)
Diastolic	65.7 (9.1)	61.8 (8.2)	63.6 (8.2)	66.9 (9.0)	64.7 (9.0)
Serum total cholesterol, mmol/L*	6.21 (1.11)	5.68 (1.12)	5.00 (0.88)	5.82 (1.00)	5.75 (1.14)
Diabetes mellitus, n (%)	64 (3.0)	36 (3.2)	232 (17.6)	121 (11.0)	453 (8.0)
Previous cardiovascular disease, n (%)	128 (6.0)	119 (10.5)	72 (5.5)	191 (17.4)	510 (9.0)
Antihypertensive drug treatment, n (%)	319 (14.9)	170 (15.0)	466 (35.4)	383 (34.9)	1338 (23.5)

Data are expressed as mean (SD) unless otherwise noted. All between-cohort differences were significant ($P \leq 0.0001$).

*To convert serum total cholesterol levels to milligrams per deciliter, divide by 0.02586.

bootstrap distribution²¹ of the so-obtained ambulatory diagnostic thresholds by randomly resampling the study population 1000 times with replacement, using the PROC SURVEYSELECT procedure, as implemented in the SAS package. For each new sample, we repeated the first 3 steps. We accounted for tied event times, caused by resampling with replacement, by the TIES=EXACT option in the

PROC PHREG procedure. Finally, we calculated the bootstrap point estimates and 95% CIs of the ambulatory thresholds as the mean \pm 1.96 SEs of the bootstrap distribution.²¹

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

TABLE 2. Hazard Ratios for Cardiovascular End Points in Relation to Conventional and Ambulatory Blood Pressure at Entry*

End points, n (%)	Cardiovascular Death	Fatal and Nonfatal Cardiovascular End Points Combined†			
		All	Stroke	Cardiac	Coronary Heart Disease
	345 (6.1)	814 (14.3)	377 (6.6)	435 (7.7)	328 (5.8)
Systolic blood pressure					
Conventional	1.11 (1.05 to 1.17)¶	1.12 (1.08 to 1.16)	1.16 (1.09 to 1.22)	1.09 (1.04 to 1.15)¶	1.07 (1.01 to 1.14)‡
24-Hour	1.22 (1.13 to 1.30)	1.24 (1.19 to 1.30)	1.32 (1.23 to 1.41)	1.20 (1.13 to 1.27)	1.17 (1.09 to 1.26)
Daytime	1.16 (1.08 to 1.24)	1.20 (1.15 to 1.25)	1.26 (1.19 to 1.35)	1.16 (1.09 to 1.23)	1.16 (1.08 to 1.25)
Nighttime	1.16 (1.10 to 1.23)	1.18 (1.14 to 1.23)	1.21 (1.15 to 1.28)	1.16 (1.10 to 1.22)	1.12 (1.05 to 1.18)¶
Diastolic blood pressure					
Conventional	1.05 (1.00 to 1.10)	1.07 (1.03 to 1.11)	1.12 (1.07 to 1.17)	1.04 (0.99 to 1.09)	1.05 (1.00 to 1.11)
24-Hour	1.18 (1.10 to 1.25)	1.18 (1.13 to 1.23)	1.27 (1.19 to 1.34)	1.11 (1.05 to 1.18)¶	1.13 (1.05 to 1.20)¶
Daytime	1.12 (1.05 to 1.19)¶	1.13 (1.09 to 1.17)	1.21 (1.14 to 1.28)	1.07 (1.01 to 1.13)‡	1.10 (1.03 to 1.17)§
Nighttime	1.14 (1.08 to 1.21)	1.15 (1.10 to 1.19)	1.20 (1.13 to 1.26)	1.10 (1.05 to 1.16)	1.10 (1.04 to 1.16)§

*The analyses included 5682 subjects.

†Hazard ratios (95% CIs) reflect the risk associated with 10- and 5-mm Hg increases in systolic and diastolic blood pressure, respectively. Hazard ratios were adjusted for cohort, sex, age, body mass index, smoking and drinking, history of cardiovascular disease, diabetes mellitus, treatment with antihypertensive drugs, and serum total cholesterol.

Significance of the hazard ratios: ‡ $P \leq 0.05$; § $P \leq 0.01$; ¶ $P \leq 0.001$; || $P \leq 0.0001$.

Results

Baseline Characteristics of Participants

Table 1 shows the baseline characteristics of each cohort. The 5682 participants included 2461 women (43.3%), 2228 patients (39.2%) with hypertensive blood pressure levels on conventional measurement, and 1338 patients (23.5%) taking blood pressure-lowering drugs. Of 4344 untreated participants, 1164 (26.8%) and 961 (22.1%) had an optimal or normal conventional blood pressure, respectively. Systolic and diastolic blood pressures were on average 0.2 mm Hg ($P=0.43$) and 1.3 mm Hg ($P\leq 0.0001$) higher on conventional than on daytime ambulatory measurement.

At enrollment, 1746 participants (30.7%) were current smokers, and 2948 (51.9%) reported intake of alcohol. Across cohorts, the prevalence of smoking (17.8% versus 43.4%), as well as that of drinking (20.0% versus 85.9%), was lowest in Ohasama and highest in Copenhagen. Between-cohort differences were significant for all variables ($P<0.0001$).

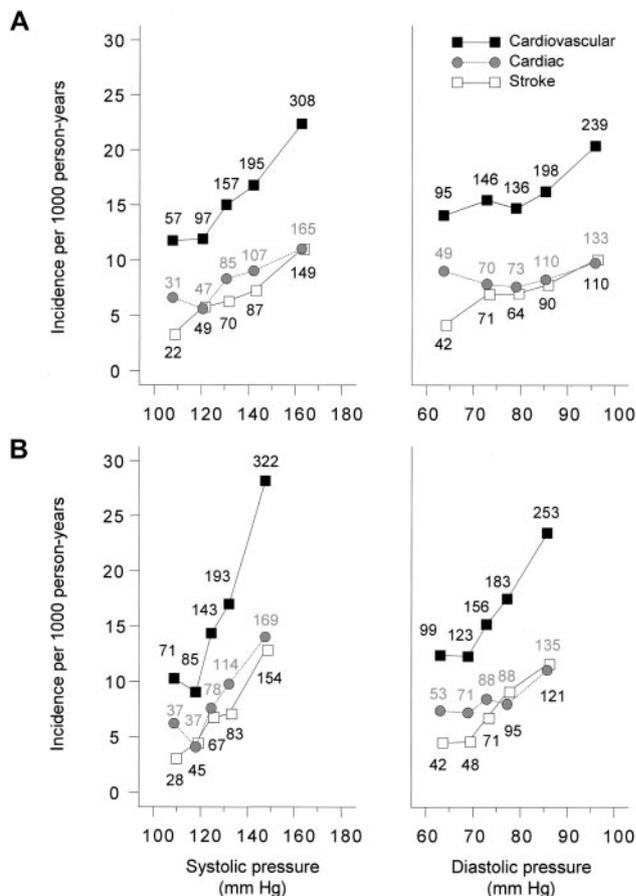
Incidence of End Points in Relation to Blood Pressure

In the overall study population, median follow-up was 9.7 years (5th to 95th percentile interval, 2.3 to 14.1 years). Across cohorts, median follow-up ranged from 9.3 years (5th to 95th percentile interval, 3.1 to 10.1 years) in Copenhagen to 13.1 years (5th to 95th percentile interval, 0.8 to 15.7 years) in Noorderkempen. Of 873 deaths (15.5 per 1000 person-years), 345 were cardiovascular, 496 were noncardiovascular, and 32 were due to unknown causes. Table 2 gives the number of cardiovascular end points in all cohorts combined. The unadjusted incidence of fatal and nonfatal cardiovascular complications averaged 15.1 events per 1000 person-years, ranging from 7.5 in Noorderkempen to 33.6 in Uppsala.

The Figure shows the increase in cardiovascular events, stroke, and cardiac end points across fifths of the distributions of the conventional and 24-hour systolic and diastolic blood pressures with standardization for cohort, sex, and age. In Cox regression, the Kolmogorov-type supremum test showed that for all outcomes in relation to blood pressure, the proportional hazards assumption was satisfied ($P>0.11$). With adjustments applied for cohort, sex, age, body mass index, smoking and drinking, history of cardiovascular disease, diabetes mellitus, treatment with antihypertensive drugs, and serum total cholesterol, blood pressure was a highly significant and consistent predictor of cardiovascular outcome, irrespective of the type of measurement (Table 2). Noncardiovascular mortality was unrelated to the conventional or 24-hour ambulatory blood pressures, with hazard ratios close to unity ($P>0.43$).

Diagnostic Thresholds for Ambulatory Blood Pressure Measurement

Using a bootstrap procedure, we calculated the ambulatory blood pressure levels that yielded 10-year absolute risks of cardiovascular, cerebrovascular, or cardiac events similar to those associated with optimal or normal blood pressure or hypertension on conventional blood pressure measurement. Table 3 shows the point estimates and 95% CIs for those risk



Incidence of cardiovascular events, stroke, and cardiac end points by fifths of the distributions of conventional office blood pressure (A) or 24-hour ambulatory blood pressure (B). Incidence rates were standardized by the direct method for cohort, sex, and age (<40, 40 to 60, and ≥ 60 years). The number of events contributing to the incidence rates is presented.

thresholds adjusted for cohort. Further adjustment for sex, age, and other cardiovascular risk factors produced consistent results (data not shown). The thresholds based on the full data set were similar to the means of the bootstraps. Table 4 provides similar risk estimates but excludes the 1338 patients who were undergoing antihypertensive drug treatment at baseline.

To obtain more easily recallable thresholds, in the last step of our analysis, we rounded the point estimates for cardiovascular events, stroke, and cardiac disease reported in Table 3 to an integer value ending in 0 or 5. Table 5 lists these rounded thresholds. In sensitivity analyses, from which we excluded 1 cohort at a time, these diagnostic thresholds remained largely consistent. After exclusion of the Uppsala cohort, the rounded thresholds for optimal systolic pressure, compared with those proposed in Table 5, were 5 mm Hg higher for whole-day (120 instead of 115 mm Hg) and daytime (125 instead of 120 mm Hg) recordings. With exclusion of the Copenhagen cohort, the rounded threshold for the daytime systolic pressure became 5 mm Hg lower (135 instead of 140 mm Hg). Rounding the values reported in Table 4 for subjects untreated at baseline also produced thresholds similar to those in Table 5, except for the optimal

TABLE 3. Ambulatory Blood Pressure Levels Yielding 10-Year Risks Similar to Those Associated With Optimal or Normal Blood Pressure or Hypertension on Conventional Measurement in All Subjects*

End Point (n)	Category	Conventional Blood Pressure, mm Hg	10-Year Absolute Risk, %	Ambulatory Blood Pressure Levels (95% CI), mm Hg		
				24-Hour	Daytime	Nighttime
Cardiovascular (814)	Optimal					
	Systolic	120	9.4	116.8 (114.6 to 119.0)	121.6 (119.1 to 124.2)	100.9 (97.5 to 104.2)
	Diastolic	80	13.1	74.2 (73.9 to 74.6)	78.9 (78.5 to 79.4)	65.3 (64.9 to 65.7)
	Normal					
	Systolic	130	11.6	123.9 (122.8 to 125.0)	129.9 (128.7 to 131.2)	110.2 (108.5 to 111.8)
	Diastolic	85	14.3	76.8 (76.3 to 77.4)	82.6 (81.9 to 83.4)	68.1 (67.5 to 68.7)
	Hypertension					
Systolic	140	14.3	131.0 (130.6 to 131.4)	138.2 (137.8 to 138.7)	119.5 (118.8 to 120.1)	
Diastolic	90	15.7	79.4 (78.2 to 80.7)	86.4 (84.5 to 88.2)	70.8 (69.4 to 72.3)	
Stroke (377)	Optimal					
	Systolic	120	4.0	117.5 (114.7 to 120.4)	122.6 (119.2 to 126.0)	100.9 (96.7 to 105.1)
	Diastolic	80	5.7	74.4 (73.8 to 74.9)	79.1 (78.4 to 79.8)	65.3 (64.6 to 65.9)
	Normal					
	Systolic	130	5.0	124.3 (122.8 to 125.8)	130.4 (128.6 to 132.2)	110.2 (108.0 to 112.3)
	Diastolic	85	6.6	77.1 (76.7 to 77.6)	82.7 (82.1 to 83.3)	68.5 (67.9 to 69.0)
	Hypertension					
Systolic	140	6.4	131.1 (130.7 to 131.5)	138.2 (137.8 to 138.7)	119.4 (118.8 to 120.0)	
Diastolic	90	7.5	79.9 (78.7 to 81.1)	86.2 (84.6 to 87.9)	71.7 (70.2 to 73.2)	
Cardiac (435)	Optimal					
	Systolic	120	4.4	115.8 (112.6 to 118.9)	120.7 (116.8 to 124.5)	99.9 (95.3 to 104.5)
	Diastolic	80	6.2	74.0 (73.6 to 74.5)	78.7 (77.9 to 79.4)	65.2 (64.7 to 65.8)
	Normal					
	Systolic	130	5.4	123.4 (121.8 to 125.0)	129.4 (127.5 to 131.4)	109.7 (107.4 to 112.0)
	Diastolic	85	6.7	76.7 (75.6 to 77.9)	83.1 (80.7 to 85.5)	67.8 (66.7 to 69.0)
	Hypertension					
Systolic	140	6.7	131.0 (130.5 to 131.4)	138.2 (137.7 to 138.8)	119.5 (118.8 to 120.2)	
Diastolic	90	7.2	79.4 (76.8 to 82.0)	87.5 (82.7 to 92.3)	70.5 (67.7 to 73.2)	

*The analyses were adjusted for cohort. Point estimates and 95% CIs were obtained from the bootstrap distribution of 1000 random samples of the study population with replacement (for further details, see Methods).

systolic levels of the 24-hour and daytime blood pressures, which became 5 mm Hg higher. The addition of a quadratic term of blood pressure to the Cox models slightly but significantly improved the fit for the 24-hour ($P \leq 0.007$) and nighttime ($P \leq 0.01$) systolic blood pressures but did not materially alter the results.

Discussion

Guidelines for the diagnosis and management of hypertension reflect consensus about the thresholds for optimal and normal blood pressure and hypertension on conventional office measurement. High-normal blood pressure on office measurement, compared with optimal blood pressure, was associated with increased rates of cardiovascular complications.²² Building on this large consensus, we used the 10-year cardiovascular risks associated with the established limits for the office blood pressure, and we rounded the so-obtained thresholds to 0 or 5 to derive more easily recallable outcome-driven blood pressure thresholds for ambulatory monitoring.

One should carefully interpret the currently proposed ambulatory thresholds. First, the relation between cardiovascular outcome and blood pressure is continuous. There is no critical level above which the risk suddenly rises. Thresholds only serve the need of clinicians to use cutoff limits for the diagnosis and management of hypertension. Second, the classification of conventional blood pressure into optimal, normal, high-normal, or hypertensive levels is not sex and age specific. In the present outcome analyses, we therefore only adjusted for cohort and disregarded sex, age, and other cardiovascular risk factors. However, further adjustment produced consistent results, with little change in the proposed ambulatory cutoff limits. Sensitivity analyses, from which we excluded 1 cohort at a time or patients taking antihypertensive drug treatment, were also largely confirmatory.

The conventional blood pressure in the present study was the average of 2 readings obtained at a single examination. More readings were available in the Belgian cohort, in which the baseline observations included 2 home visits at an interval

TABLE 4. Ambulatory Blood Pressure Levels Yielding 10-Year Risks Similar to Those Associated With Optimal or Normal Blood Pressure or Hypertension on Conventional Measurement in 4344 Subjects Untreated at Baseline*

End Point (n)	Category	Conventional Blood Pressure, mm Hg	10-Year Absolute Risk, %	Ambulatory Blood Pressure Levels (95% CIs), mm Hg		
				24-Hour	Daytime	Nighttime
Cardiovascular (462)	Optimal					
	Systolic	120	7.5	118.8 (116.6 to 121.0)	125.5 (123.2 to 127.8)	103.2 (99.6 to 106.9)
	Diastolic	80	9.9	74.4 (74.1 to 74.8)	79.6 (79.2 to 79.9)	65.5 (65.1 to 65.9)
	Normal					
	Systolic	130	9.3	125.3 (124.4 to 126.2)	132.5 (131.5 to 133.4)	112.1 (110.8 to 113.5)
	Diastolic	85	10.7	76.4 (75.5 to 77.3)	82.1 (81.0 to 83.2)	67.6 (66.6 to 68.6)
	Hypertension					
	Systolic	140	11.5	131.9 (131.1 to 132.6)	139.5 (138.7 to 140.2)	121.0 (119.7 to 122.3)
	Diastolic	90	11.6	78.3 (76.7 to 80.0)	84.6 (82.5 to 86.8)	69.7 (67.7 to 71.6)
Stroke (204)	Optimal					
	Systolic	120	3.2	119.5 (116.7 to 122.3)	126.6 (123.7 to 129.4)	103.6 (99.2 to 108.1)
	Diastolic	80	4.4	74.7 (74.2 to 75.2)	79.8 (79.2 to 80.4)	65.8 (65.3 to 66.4)
	Normal					
	Systolic	130	4.0	125.7 (124.5 to 127.0)	133.0 (131.7 to 134.3)	112.3 (110.5 to 114.1)
	Diastolic	85	4.9	76.8 (75.9 to 77.7)	82.5 (81.4 to 83.6)	68.1 (67.1 to 69.1)
	Hypertension					
	Systolic	140	5.1	132.0 (131.2 to 132.7)	139.5 (138.8 to 140.2)	120.9 (119.8 to 122.1)
	Diastolic	90	5.4	78.9 (77.1 to 80.7)	85.1 (82.8 to 87.5)	70.3 (68.3 to 72.3)
Cardiac (249)	Optimal					
	Systolic	120	3.2	117.6 (114.5 to 120.7)	124.3 (120.8 to 127.7)	101.5 (96.3 to 106.7)
	Diastolic	80	4.3	74.2 (73.8 to 74.6)	79.4 (78.9 to 79.8)	65.2 (64.7 to 65.7)
	Normal					
	Systolic	130	4.0	124.8 (123.6 to 126.1)	132.0 (130.6 to 133.4)	111.5 (109.5 to 113.4)
	Diastolic	85	4.6	76.6 (74.9 to 78.2)	82.4 (80.2 to 84.6)	67.9 (65.9 to 69.9)
	Hypertension					
	Systolic	140	4.9	132.1 (131.2 to 133.0)	139.7 (138.8 to 140.7)	121.4 (119.7 to 123.2)
	Diastolic	90	5.0	78.9 (75.6 to 82.2)	85.5 (81.0 to 89.9)	70.6 (66.5 to 74.6)

*The analyses were adjusted for cohort. Point estimates and 95% CIs were obtained from the bootstrap distribution of 1000 random samples of the study population with replacement (for further details, see Methods).

of 2 to 4 weeks.²³ At each visit, the observers obtained 5 consecutive blood pressure readings. Blood pressure significantly decreased from the first to the second home visit, but the average difference was only ≈ 2 mm Hg for both systolic and diastolic blood pressures. Lack of repeated conventional blood pressure measurements at different occasions in the other cohorts precluded a correction for regression dilution bias of the association between cardiovascular outcome and the conventional blood pressure; however, the small differences between the repeated measurements in the Belgian

cohort²³ suggest that such correction would not greatly affect the present results.

Previous studies^{24–27} in hypertensive patients based their definitions of a normal ambulatory blood pressure on noninvasive²⁷ or intra-arterial²⁵ 24-hour recordings or on daytime recordings^{24,26} spanning periods ranging from 10 hours²⁶ to 16 hours.²⁴ The thresholds of normality in studies of hypertensive patients that used an intermittent technique of ambulatory monitoring ranged from 131 mm Hg²⁴ to 140 mm Hg²⁶ systolic and from 86 mm Hg²⁴ to 90 mm Hg²⁶ diastolic in daytime recordings. The aforementioned studies in hypertensive patients, although outcome driven, are difficult to interpret, because blood pressure was not analyzed as a continuous variable,^{25,27} because some studies^{25,26} did not include a normotensive control group, or because investigators did not attempt to further subdivide the normotensive control subjects into those with normal or elevated ambulatory blood pressure.^{24,27}

Four population-based reports^{6,7,10,28} used outcome data to address normality of the ambulatory blood pressure. In a cross-sectional observational study of the population of

TABLE 5. Proposal for Outcome-Driven Reference Values for Ambulatory Blood Pressure Measurement*

	24-Hour	Daytime	Nighttime
Optimal blood pressure, mm Hg	<115/75	<120/80	<100/65
Normal blood pressure, mm Hg	<125/75	<130/85	<110/70
Ambulatory hypertension, mm Hg	$\geq 130/80$	$\geq 140/85$	$\geq 120/70$

Threshold values were obtained by rounding the point estimates reported in Table 3 to an integer value ending in 0 or 5.

Monza, Italy, Sega and colleagues⁵ regressed ambulatory on office blood pressure. They found that the cutoff limits of the 24-hour blood pressure that corresponded with office hypertension were 125 mm Hg systolic and 76 mm Hg diastolic.⁵ Follow-up of the Monza cohort demonstrated that total and cardiovascular mortality gradually increased from sustained normotension over white-coat and masked hypertension to sustained hypertension.¹⁰ Two Scandinavian population studies^{6,7} used as thresholds of normality daytime blood pressure levels of 135 mm Hg systolic and 85 mm Hg diastolic. Ohkubo and coworkers²⁸ observed that the optimal 24-hour blood pressure that resulted in the lowest all-cause mortality ranged from 120 to 133 mm Hg systolic and from 65 to 78 mm Hg diastolic. Levels above and below these 24-hour thresholds were associated with higher cardiovascular or noncardiovascular mortality, respectively.²⁸ Of the 4 studies,^{6,7,10,28} only the Ohasama report²⁸ proposed cutoff limits directly derived from outcome. The introduction of stroke units and the wide availability of invasive coronary care and thrombolysis recently reduced the case-fatality rate of most cardiovascular complications of hypertension. The lack of accounting for nonfatal events^{10,28} and the low number of exclusively fatal cardiovascular end points in some studies (n=69)¹⁰ therefore limits the generalizability of the previous reports.

The present study must be interpreted within the context of its potential limitations. First, the present analysis rested only on 4 population-based cohorts and might therefore not be representative for non-European or non-Japanese subjects. Second, our study population predominantly included older adults. Of the participants, only 2.1% and 5.9% were younger than 30 or 40 years, respectively. The Uppsala cohort⁶ consisted only of men. Anthropometric characteristics differed between cohorts. The high prevalence of smoking probably explained why the daytime blood pressure was higher in the Copenhagen cohort than the conventional blood pressure.²⁹ Ambulatory blood pressure monitoring was not standardized in terms of device type and intervals between readings. On the other hand, the use of a single SAS macro ensured that daytime and nighttime periods were always defined in the same fashion, using short, fixed clock-time intervals,^{9,17} and that the time-weighted means over all periods of the day were calculated identically across cohorts. Finally, the rounded blood pressure thresholds are a compromise between accuracy and practicability. Whenever rounding suggested different thresholds (± 5 mm Hg), we always opted for the lowest value.

In conclusion, the present report provides point estimates with 95% CIs for 3 major cardiovascular end points in relation to the ambulatory blood pressure. The systolic/diastolic cutoff limits for normality in the current guidelines for the management of hypertension are 125/80 mm Hg for 24-hour blood pressure in Europe¹ and 135/85 mm Hg and 120/75 mm Hg for awake and asleep blood pressures in the United States.^{2,15} The present findings suggest that outcome-driven thresholds for optimal and normal levels of the ambulatory blood pressure are lower than those currently proposed by hypertension guidelines.

Acknowledgments

The authors gratefully acknowledge the expert assistance of Sandra Covens, Linda Custers, Marie-Jeanne Jehoul, Katrien Staessen, Hanne Truyens, and Renilde Wolfs (Leuven, Belgium).

Sources of Funding

The European Union (grants IC15-CT98-0329-EPOGH and LSHM-CT-2006-037093), the Fonds voor Wetenschappelijk Onderzoek Vlaanderen, Ministry of the Flemish Community, Brussels, Belgium (grants G.0424.03 and G.0575.06), and the Katholieke Universiteit Leuven, Belgium (grants OT/99/28, OT/00/25 and OT/05/49) gave support to the Studies Coordinating Centre. Dr Staessen holds the Pfizer Chair for Hypertension and Cardiovascular Research (<http://www.kuleuven.be/mecenaat/leerstolen/overzicht.htm>). The Ministries of Education, Culture, Sports, Science and Technology (grants 15790293, 17790382, 18390192, and 18590587) and of Health, Labor and Welfare (health science research grants and medical technology evaluation research grants), grant-in-aid from the Japanese Society for the Promotion of Science (16.54041 and 18.54042), the Japan Atherosclerosis Prevention Fund, the Uehara Memorial Foundation, and the Takeda Medical Research Foundation supported research in Japan. The Danish Heart Foundation (grant 01-2-9-9A-22914), the Beckett Fonden, and the Lundbeck Fonden supported the studies in Copenhagen.

Disclosures

None.

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CLINICAL PERSPECTIVE

Although blood pressure is continuously distributed, clinicians need a diagnostic reference frame to interpret ambulatory blood pressure values and to classify patients. The systolic/diastolic cutoff limits for normality in the current guidelines for the management of hypertension are 125/80 mm Hg for 24-hour blood pressure in Europe and 135/85 mm Hg and 120/75 mm Hg, respectively, for awake and asleep blood pressures in the United States. The currently proposed levels for an optimal blood pressure on ambulatory monitoring are substantially lower than the thresholds recommended in the guidelines. The diagnostic blood pressure levels based on population studies should be further validated in event-based studies set up in referred patients with a traditional office diagnosis of hypertension. It is indeed in these patients that the ambulatory thresholds will be predominantly used for risk stratification. Until this evidence becomes available, the population-based thresholds might inform guidelines and help clinicians in the management of patients with suspected or established hypertension.