Prognostic value of isolated nocturnal hypertension on ambulatory measurement in 8711 individuals from 10 populations

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Background **We and other investigators previously reported that isolated nocturnal hypertension on ambulatory measurement (INH) clustered with cardiovascular risk factors and was associated with intermediate target organ damage. We investigated whether INH might also predict hard cardiovascular endpoints.**

Methods and results **We monitored blood pressure (BP) throughout the day and followed health outcomes in 8711 individuals randomly recruited from 10 populations (mean age 54.8 years, 47.0% women). Of these, 577 untreated individuals had INH (daytime BP <135/85 mmHg and night-time BP ≥120/70 mmHg) and 994 untreated individuals had isolated daytime hypertension on ambulatory measurement (IDH; daytime BP ≥135/85 mmHg and night-time BP <120/70 mmHg). During follow-up (median 10.7 years), 1284 deaths (501 cardiovascular) occurred and 1109 participants experienced a fatal or nonfatal cardiovascular event. In multivariable-adjusted analyses, compared with normotension ($n = 3837$), INH was associated with a higher risk of total mortality (hazard ratio 1.29, $P = 0.045$) and all cardiovascular events (hazard ratio 1.38, $P = 0.037$). IDH was associated with increases in all cardiovascular events (hazard ratio 1.46, $P = 0.0019$) and cardiac endpoints (hazard ratio 1.53, $P = 0.0061$). Of 577 patients with INH, 457 were normotensive (<140/90 mmHg) on office BP measurement. Hazard ratios associated with INH with additional adjustment for office BP were 1.31 ($P = 0.039$) and 1.38 ($P = 0.044$) for total mortality and all cardiovascular events, respectively. After exclusion of patients with office hypertension, these hazard ratios were 1.17 ($P = 0.31$) and 1.48 ($P = 0.034$).**

Conclusion **INH predicts cardiovascular outcome in patients who are normotensive on office or on ambulatory daytime BP measurement.** *J Hypertens* **28:2036–2045**

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Keywords: ambulatory blood pressure, epidemiology, population science, risk factors

Abbreviations: BP, blood pressure; CI, confidence interval; IDACO, the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes; IDH, isolated daytime hypertension on ambulatory measurement; INH, isolated nocturnal hypertension on ambulatory measurement

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Introduction

In 2007, we described isolated nocturnal hypertension on ambulatory measurement (INH) as a potentially novel clinical entity [1]. Among 677 Chinese randomly recruited from a rural area, 74 (10.9%) had, on ambulatory monitoring, an elevated night-time blood pressure (BP) (≥120/70 mmHg) in the presence of a normal daytime BP (<135/85 mmHg) [1]. Of the 74 patients, only four (5.4%) had hypertension on office BP measurement (≥140/90 mmHg), which highlighted that automated BP measurement during sleep was required to diagnose INH. Along similar lines, Hoshide *et al.* [2] reported an elevated night-time BP (≥120/75 mmHg) in the presence of a normal self-measured home BP (<135/85 mmHg) in 17 (10.3%) of 165 community-dwelling individuals. Wijkman *et al.* [3] also observed nocturnal hypertension (≥120/70 mmHg) but a normal clinic BP (<130/80 mmHg) among 30 (7.2%) of 414 type-2 diabetic patients. In analyses of the International Database of the Ambulatory Blood Pressure [4], we noticed that the prevalence of INH was higher among South Africans of black ancestry (10.2%) and Japanese (10.9%) than in Western (6.0%) and Eastern (7.9%) Europeans [1].

In previous studies, INH was associated with clustering of cardiovascular risk factors [1], thickening of the carotid intima–media [2], left ventricular remodeling [2], and increased arterial stiffness, as reflected by aortic pulse wave velocity [1,3], the central and peripheral augmentation indexes [1], and the ambulatory arterial stiffness index [1]. However, the major question whether INH might also predict a worse cardiovascular outcome in terms of hard endpoints remains unanswered. To address this issue, we analyzed the International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome (IDACO) [5–8].

Methods

Study population

As described in detail elsewhere [5–8], we constructed the IDACO database. Studies were eligible for inclusion, if they involved a random population sample, if baseline information on ambulatory BP and cardiovascular risk factors was available, and if the subsequent follow-up included fatal and nonfatal outcomes. Of 13 studies [9–19], we excluded two [18,19] because at the time of writing of this manuscript follow-up had not yet been organized [19] or because follow-up did not include nonfatal events [18]. All studies received ethical approval and have been reported in peer-reviewed publications.

At the time of writing of this report, the IDACO database included 11 785 individuals enrolled in prospective population studies at 11 centers [9–17]. For the present analysis, we selected studies in which all the necessary data, including ambulatory BPs, biochemical measurements, and outcome data, were available, leaving 10 cohorts [10–17] and 10 805 individuals for possible analysis. In line with previous reports [7–8], we excluded 250 participants because they were below 18 years, and 1844 participants because they had fewer than 10 daytime or five night-time BP readings. The 8711 analyzed participants included: 1127 from Noorderkempen, Belgium [10]; 351 from the JingNing county, China [15]; 165 from Pilsen, the Czech Republic [14]; 2142 from Copenhagen, Denmark [16]; 310 from Padova, Italy [14]; 1526 from Ohasama, Japan [13]; 308 from Kraków, Poland [14]; 244 from Novosibirsk, the Russian Federation [12,14]; 1100 older men from Uppsala, Sweden [17]; and 1438 individuals from Montevideo, Uruguay [11]. All participants gave informed written consent.

Blood pressure measurements

Conventional BP was measured by trained observers with a mercury sphygmomanometer [10,12,14–17], with validated auscultatory [13] (USM-700F; UEDA Electronic Works, Tokyo, Japan) or oscillometric [11] (OMRON HEM-705CP; Omron Corporation, Tokyo, Japan) devices, using the appropriate cuff size, with the participants in the sitting [10–16] or supine [17] position. Conventional BP was the average of two consecutive readings obtained either at the participants' homes [10–12,14,15] or at an examination center [13,16,17]. Hypertension was a conventional SBP of at least 140 mmHg or DBP of 90 mmHg at a single visit or use of antihypertensive drugs [20].

We programmed portable monitors to obtain ambulatory BP readings at 30-min intervals throughout the whole day [13] or at intervals ranging from 15 [16] to 30 [17] minutes during daytime and from 30 [16] to 60 [17] minutes at night. The devices implemented an auscultatory algorithm (Accutracker II; Suntech Medical Instruments, North Carolina, USA) in Uppsala [17] or an oscillometric technique (SpaceLabs 90202 and 90207, SpaceLabs Medical Inc., Redmond, Washington, USA; Takeda TM-2421, A&D Instruments, Tokyo, Japan; and ABPM 630, Nippon Colin, Komaki, Japan) in the other cohorts [10–16].

The same Statistical Analysis System (SAS; SAS Institute, Cary, North Carolina, USA) macro processed all ambulatory recordings, which generally stayed unedited. The Ohasama recordings were edited sparsely according to previously published criteria [21]. While accounting for the daily pattern of activities of the participants, we defined daytime as the interval from 1000 to 2000 h in Europeans [10,12,14,16,17] and South Americans [11], and from 0800 to 1800 h in Asians [13,15]. The corresponding night-time intervals ranged from midnight to 0600 h [10–12,14,16,17] and from 2200 to 0400 h [13,15], respectively. These fixed time intervals eliminate the transition periods in the morning and evening when BP changes rapidly, resulting in daytime and night-time BP levels that are within 1–2 mmHg of the awake and asleep levels [15,22]. Within individual participants, we

weighted the means of the ambulatory BP by the interval between readings.

In line with published diagnostic thresholds of ambulatory normotension [23], we defined nocturnal hypertension as a night-time BP of at least 120 mmHg SBP or 70 mmHg DBP. Daytime hypertension was a diurnal BP of at least 135 mmHg SBP or 85 mmHg DBP. On the basis of these cutoff limits of the ambulatory BP and treatment status, we classified patients into four groups: untreated individuals, who were normotensive during daytime and night-time; untreated individuals with isolated daytime hypertension on ambulatory measurement (IDH); untreated individuals with INH; and patients with hypertension sustained during daytime and night-time or on treatment for hypertension irrespective of their BP level during daytime or night-time.

Other measurements

We used the questionnaires originally administered in each cohort to obtain information on each participant's medical history, and smoking and drinking habits. BMI was body weight in kilograms divided by height in meters squared. We measured serum cholesterol and blood glucose by automated enzymatic methods. Diabetes mellitus was the use of antidiabetic drugs, a fasting blood glucose concentration of at least 7.0 mmol/l [10–17], a random blood glucose concentration of at least 11.1 mmol/l [10,13,15], a self-reported diagnosis [10,11,13], or diabetes documented in practice or hospital records [11].

Ascertainment of events

We ascertained vital status and the incidence of fatal and nonfatal diseases from the appropriate sources in each country, as described in previous publications [5–8]. Fatal and nonfatal stroke did not include transient ischemic attack. Coronary events encompassed death from ischemic heart disease, sudden death, nonfatal myocardial infarction (MI), and coronary revascularization. Cardiac events comprised coronary endpoints and fatal and nonfatal heart failure. The composite cardiovascular endpoint included all aforementioned endpoints and 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 9.1.3 (SAS Institute). For comparison of means and proportions, we applied the large-sample z-test and the $\chi 2$-statistic, respectively. After stratification for cohort and sex, we interpolated missing values of BMI ($n = 17$) and total serum cholesterol ($n = 121$) from the regression slope on age. In individuals with unknown drinking ($n = 786$) or smoking habits ($n = 39$), or with unknown status of diabetes ($n = 3$), we set the design variable to the cohort and sex-specific mean of the codes (0,1). Statistical significance was an α-level of less than 0.05 on two-sided tests.

We first tabulated the incidence of endpoints by BP status on ambulatory measurement. We reported crude rates and rates standardized by the direct method for cohort, sex, and age ($\leq$40, 40–60, and $\geq$60 years). We used Kaplan–Meier survival function estimates, plotted according to current recommendations [24], and the log-rank test to compare incidence rates by BP group. We used Cox regressions to compute hazard ratios associated with each ambulatory hypertensive group relative to the normotensive group for mortality and for fatal and nonfatal outcomes combined. The hazard ratios were stratified for cohort and adjusted for sex, age (treated as a continuous variable), BMI (continuous), smoking (0, 1) and drinking (0, 1), serum cholesterol (continuous), history of cardiovascular disease (0, 1), and diabetes mellitus (0, 1). While stratifying for cohort, we pooled the cohorts recruited in the framework of the European Project on Genes in Hypertension [14]. We tested heterogeneity in the hazard ratios across subgroups by introducing the appropriate interaction term in the Cox models. To test the prognostic significance of nocturnal BP in individuals with normal daytime BP on office or on ambulatory BP measurement, we modeled the probability of the 10-year incidence of total mortality and fatal and nonfatal cardiovascular events using the Weibull distribution for time-failure data.

Results

Baseline characteristics

The study population consisted of 5396 Europeans (61.9%), 1877 Asians (21.6%), and 1438 South Americans (16.5%). The 8711 participants included 4096 women (47.0%) and 3532 patients with office hypertension (40.6%), of whom 1899 (53.8%) were taking BP-lowering drugs. Mean ($\pm$SD) age was 54.8 $\pm$ 15.1 years. At enrollment, 2491 participants (28.6%) were current smokers and 4126 (47.4%) reported intake of alcohol.

Of 8711 participants, 3837 (44.1%) were normotensive during daytime and night-time, 994 (11.4%) had IDH, 577 (6.6%) had INH, and 3303 (37.9%) had sustained hypertension. Table 1 shows the baseline characteristics of the participants according to their BP status. The prevalence of INH was significantly higher ($P < 0.05$) in South Americans (9.4%) than in Asians (7.2%) and Europeans (5.7%). Compared with individuals with ambulatory normotension, patients with INH were older, more likely to be men, and more frequently reported alcohol intake. They also had a higher BMI, a faster pulse rate at night, and higher serum cholesterol and blood glucose. The 577 patients with INH included 150 (26.0%) with isolated systolic hypertension, 233 (40.4%) with isolated diastolic hypertension, and 194 (33.6%) with systolic and diastolic hypertension. Of the

Table 1 Baseline characteristics of participants

Characteristics	Normotension	Isolated nocturnal hypertension	Isolated daytime hypertension	Sustained hypertension
Number of participants	3837	577	994	3303
European	2303 (60.0)	307 (53.2)†	747 (75.2)†	2039 (61.7)
Asian	814 (21.2)	135 (23.4)	129 (12.9)†	799 (24.2)†
South American	720 (18.8)	135 (23.4)†	118 (11.9)†	465 (14.1)‡
Women	2167 (56.5)	224 (38.8)‡	353 (35.5)‡	1352 (40.9)‡
Smokers	1131 (29.5)	179 (31.0)	331 (33.3)*	850 (25.7)†
Drinking alcohol	1602 (41.8)	274 (47.5)†	581 (58.5)‡	1669 (50.5)‡
Office hypertension	311 (8.1)	120 (20.8)‡	361 (36.3)‡	2740 (83.0)‡
On antihypertensive treatment	0	0	0	1899 (57.5)
Diabetes mellitus	157 (4.1)	31 (5.4)	61 (6.1)†	373 (11.3)‡
Cardiovascular disorders	168 (4.4)	37 (6.4)*	59 (5.9)*	496 (15.0)‡
Age (years)	48.5 ± 15.1	54.9 ± 15.2‡	55.9 ± 14.0‡	61.7 ± 11.9‡
BMI (kg/m^2)	24.4 ± 3.7	25.4 ± 4.2‡	26.2 ± 4.0‡	26.6 ± 4.5‡
Conventional BP (mmHg)				
Systolic	119.4 ± 14.4	129.1 ± 15.8‡	134.9 ± 15.7‡	145.0 ± 19.9‡
Diastolic	74.1 ± 9.0	78.9 ± 9.2‡	82.4 ± 9.3‡	86.1 ± 11.9‡
Ambulatory measurements				
24-h SBP (mmHg)	113.8 ± 7.4	124.2 ± 6.8‡	128.2 ± 6.3‡	135.2 ± 14.2‡
24-h DBP (mmHg)	68.4 ± 5.0	75.1 ± 5.1‡	75.9 ± 5.0‡	79.2 ± 9.1‡
Daytime SBP (mmHg)	120.1 ± 8.4	125.1 ± 6.9‡	139.8 ± 7.8‡	141.1 ± 15.2‡
Daytime DBP (mmHg)	73.5 ± 5.8	76.6 ± 5.8‡	83.9 ± 6.3‡	83.9 ± 10.0‡
Daytime pulse rate (bpm)	78.6 ± 10.0	78.3 ± 10.3	79.2 ± 10.4	76.4 ± 11.2‡
Night-time SBP (mmHg)	102.7 ± 7.8	121.1 ± 9.2‡	109.3 ± 6.8‡	123.9 ± 16.1‡
Night-time DBP (mmHg)	59.3 ± 5.4	71.8 ± 6.1‡	62.5 ± 4.6‡	70.6 ± 9.9‡
Night-time pulse rate (bpm)	63.3 ± 9.0	65.6 ± 10.7‡	63.7 ± 9.3	63.6 ± 9.7
Serum cholesterol (mmol/l)	5.45 ± 1.14	5.54 ± 1.19‡	5.87 ± 1.16‡	5.76 ± 1.14‡
Blood glucose (mmol/l)	4.95 ± 0.98	5.30 ± 1.69‡	5.21 ± 1.23‡	5.54 ± 1.68‡

Data are means (±SD) or number (%). Office hypertension was a conventional SBP of at least 140 mmHg or DBP of 90 mmHg, or use of antihypertensive drugs. Blood glucose was available in 2905 normotensive individuals, 449 with isolated nocturnal hypertension, 855 with isolated daytime hypertension, and 2671 with sustained hypertension. Differences among the four groups were significant ($P < 0.001$) for all the characteristics. Significance of the difference with the normotensive reference group: *$P < 0.05$, †$P < 0.01$, and ‡$P < 0.001$. BP, blood pressure.

577 patients with INH, only 120 (20.8%) were diagnosed as being hypertensive on conventional BP measurement.

Incidence of events

In the overall study population, median follow-up was 10.7 years (5th to 95th percentile interval 2.5–15.4 years). Across cohorts, median follow-up ranged from 2.5 years (5th to 95th percentile interval 2.3–2.6 years) in JingNing to 13.3 years (5th–95th percentile interval 4.7–16.3 years) in Noorderkempen. During 87 203 person-years of follow-up, 1284 participants died (14.7 per 1000 person-years) and 1109 experienced a fatal or nonfatal cardiovascular complication (13.2 per 1000 person-years). Mortality included 501 cardiovascular and 742 noncardiovascular deaths and 41 deaths from unknown cause (Table 2). Considering cause-specific first cardiovascular events, the incidence of fatal and nonfatal stroke amounted to 145 and 391, respectively. Cardiac events consisted of 176 fatal and 442 nonfatal events, including 76 fatal and 214 nonfatal cases of acute MI, 32 deaths from ischemic heart disease, 28 sudden deaths, 40 fatal and 171 nonfatal cases of heart failure, and 57 cases of surgical or percutaneous coronary revascularization.

Risk associated with subtypes of ambulatory hypertension

Table 2 shows the crude and cohort, sex, and age-standardized rates of mortality and combined fatal and nonfatal events by subtypes of ambulatory hypertension. The Kaplan–Meier survival function estimates for total mortality and for all fatal combined with nonfatal cardiovascular events according to BP classification appear in Fig. 1. Compared with normotensive individuals, patients with IDH, INH, or sustained hypertension had a significantly higher ($P < 0.05$) incidence of mortality and morbidity (Table 2).

Table 3 provides unadjusted and adjusted hazard ratios associated with the three categories of ambulatory hypertension relative to the normotensive control group. With cumulative adjustments applied for cohort, sex, age, BMI, smoking and drinking, serum cholesterol, diabetes, and history of cardiovascular disease, INH was associated with an increased risk for total mortality (hazard ratio 1.29, $P = 0.045$) and all cardiovascular events (hazard ratio 1.38, $P = 0.037$). The hazard ratios for cardiovascular mortality (1.30, $P = 0.29$), cardiac events (1.41, $P = 0.096$), and stroke (1.21, $P = 0.46$) were of similar magnitude but did not reach statistical significance because of the relatively low number of events for these endpoints. With similar adjustments applied, IDH was associated with significant increases in all cardiovascular events (hazard ratio 1.46, $P = 0.0019$) and cardiac endpoints (hazard ratio 1.53, $P = 0.0061$), but not total mortality (hazard ratio 1.07, $P = 0.56$), cardiovascular mortality (hazard ratio 1.38, $P = 0.091$), and

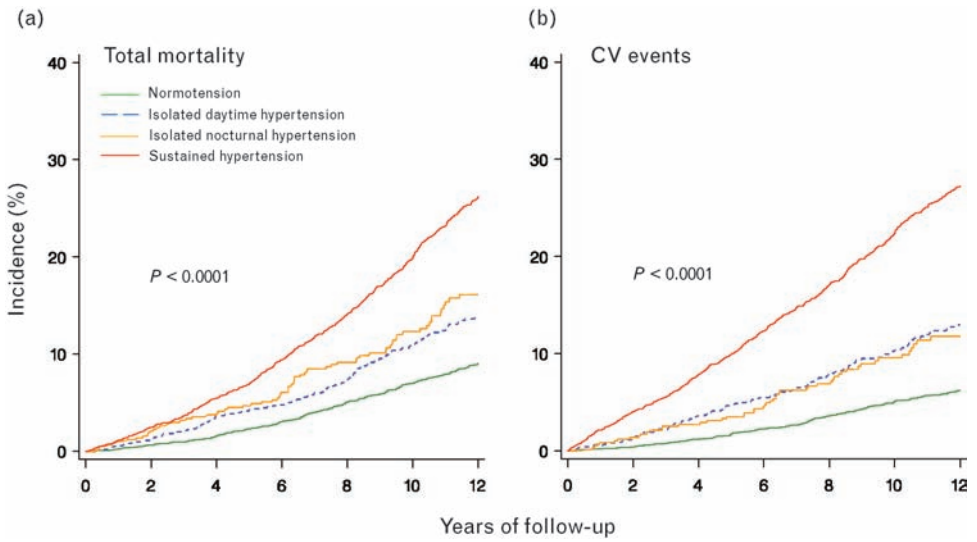
Table 2 Incidence of events by ambulatory blood pressure status

	Normotension	Isolated nocturnal hypertension	Isolated daytime hypertension	Sustained hypertension
Number of participants	3837	577	994	3303
All-causes mortality				
Number of deaths	295	81	128	780
Crude rate	7.6 (6.7–8.4)	14.7 (11.5–17.9)‡	12.4 (10.3–14.6)‡	24.1 (22.4–25.8)‡
Standardized rate	10.6 (5.9–15.3)	13.9 (2.2–25.6)	11.2 (3.3–19.1)	18.5 (11.6–25.4)
Cardiovascular mortality				
Number of deaths	76	22	46	357
Crude rate	1.9 (1.5–2.4)	4.0 (2.6–5.7)†	4.5 (3.2–5.8)‡	11.0 (9.9–12.2)‡
Standardized rate	2.8 (0.7–4.9)	3.9 (0–8.7)	4.3 (0–9.0)	8.5 (4.1–12.8)
Noncardiovascular mortality				
Number of deaths	210	55	76	401
Crude rate	5.4 (4.6–6.1)	10.0 (7.3–12.6)‡	7.4 (5.7–9.1)*	12.4 (11.2–13.6)‡
Standardized rate	7.5 (3.7–11.3)	9.3 (0.7–17.8)	6.5 (1.4–11.7)	9.2 (5.3–13.1)
All cardiovascular events				
Number of events	188	54	112	755
Crude rate	4.9 (4.2–5.6)	10.1 (7.4–12.8)‡	11.2 (9.2–13.3)‡	25.1 (23.3–26.9)‡
Standardized rate	7.0 (3.3–10.7)	9.7 (0.3–19.2)	11.1 (0.9–21.3)	20.1 (12.4–27.8)
Cardiac events				
Number of events	108	31	73	406
Crude rate	2.8 (2.3–3.3)	5.7 (3.7–7.7)†	7.2 (5.6–8.9)‡	13.0 (11.8–14.3)‡
Standardized rate	4.0 (1.3–6.8)	5.6 (0–12.0)	6.5 (0.2–12.9)	10.7 (5.6–15.9)
Stroke				
Number of strokes	78	20	39	344
Crude rate	2.0 (1.6–2.5)	3.7 (2.1–5.3)*	3.8 (2.6–5.0)†	11.0 (9.9–12.2)‡
Standardized rate	2.7 (0.7–4.7)	3.4 (0–8.3)	4.4 (0–9.4)	8.5 (4.0–13.0)

Values are rates (95% confidence interval), expressed as number of events per 1000 person-years. Rates are crude or standardized for cohort, sex, and age (≤40, 40–60, and ≥60 years) by the direct method. Significance of the difference with the normotensive reference group: *$P<0.05$, †$P<0.01$, and ‡$P<0.001$.

stroke (hazard ratio 1.35, $P=0.13$). The multivariable-adjusted hazard ratios associated with sustained hypertension (Table 3) were significant for total mortality (1.51, $P<0.0001$), cardiovascular mortality (2.19, $P<0.0001$), all cardiovascular events (2.48, $P<0.0001$), cardiac events (2.30, $P<0.0001$), and stroke (2.64, $P<0.0001$). After exclusion of 1899 treated patients from the sustained hypertensive group, the hazard ratios for 1404 patients with elevated BP values during day and night were 1.47 [95% confidence interval (CI) 1.23–1.76, $P<0.0001$) for total mortality, 2.16 (95% CI 1.58–2.95, $P<0.0001$) for cardiovascular mortality, 2.33 (95% CI 1.91–2.84, $P<0.0001$) for all cardiovascular events, 1.94 (95% CI 1.49–2.53, $P<0.0001$) for cardiac

Fig. 1



Cumulative incidence of total mortality (a) and all cardiovascular events (b) by ambulatory blood pressure status. *P* values are for the differences among the four categories by log-rank test.

Table 3 Hazard ratios by categories of ambulatory hypertension

Outcomes	Isolated nocturnal hypertension	Isolated daytime hypertension	Sustained hypertension
All-causes mortality (1284)	81	128	780
Unadjusted	1.99 (1.56–2.55)‡	1.67 (1.35–2.05)‡	3.26 (2.85–3.73)‡
Adjusted	1.29 (1.01–1.65)*	1.07 (0.86–1.32)	1.51 (1.31–1.74)‡
Cardiovascular mortality (501)	22	46	357
Unadjusted	2.10 (1.31–3.38)†	2.32 (1.61–3.35)‡	5.78 (4.51–7.40)‡
Adjusted	1.30 (0.80–2.09)	1.38 (0.95–2.00)	2.19 (1.69–2.85)‡
Noncardiovascular mortality (742)	55	76	401
Unadjusted	1.89 (1.41–2.55)‡	1.38 (1.07–1.80)*	2.35 (1.98–2.77)‡
Adjusted	1.23 (0.91–1.66)	0.90 (0.69–1.18)	1.19 (0.99–1.43)
All cardiovascular events (1109)	54	112	755
Unadjusted	2.08 (1.53–2.81)‡	2.28 (1.81–2.89)‡	5.16 (4.40–6.06)‡
Adjusted	1.38 (1.02–1.87)*	1.46 (1.15–1.85)†	2.48 (2.10–2.94)‡
Cardiac events (618)	31	73	406
Unadjusted	2.05 (1.38–3.06)‡	2.56 (1.91–3.45)‡	4.66 (3.77–5.76)‡
Adjusted	1.41 (0.94–2.10)	1.53 (1.13–2.07)†	2.30 (1.84–2.88)‡
Stroke (481)	20	39	344
Unadjusted	1.85 (1.13–3.02)†	1.90 (1.29–2.78)†	5.52 (4.32–7.06)‡
Adjusted	1.21 (0.74–1.98)	1.35 (0.91–2.00)	2.64 (2.04–3.43)‡

Hazard ratios (95% confidence intervals) express the risk relative to the normotensive group. Numbers of cases are given for each endpoint. The cause of death was unknown in 41 cases. Cox models were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease and diabetes mellitus. Significance of the hazard ratios: *$P<0.05$, †$P<0.01$, and ‡$P<0.001$.

events, and 2.73 (95% CI 2.00–3.73, $P<0.0001$) for stroke.

Sensitivity analyses

Sensitivity analyses (Table 4) involving total mortality and all cardiovascular events in relation to INH did not show significant heterogeneity in the hazard ratios ($0.08 \leq P \leq 0.89$) according to baseline characteristics, including ethnicity, sex, median age (<60 or ≥60 years), BMI (<25 or ≥25 kg/m^2), current smoking (0, 1), drinking alcohol (0, 1), or history of cardiovascular disease (0, 1). The only exception was the risk of all cardiovascular events associated with INH in smokers versus nonsmokers [hazard ratios (95% CI) 0.80 (0.43–1.47) versus 1.78 (95% 1.25–2.55), $P=0.016$]. After further adjustment for daytime SBP and DBP in addition to the covariables we had considered in the multivariable Cox models, INH still carried a higher risk for total mortality [hazard ratio 1.28 (95% CI 1.00–1.64), $P=0.049$] and for all cardiovascular events [hazard ratio 1.34 (95% CI 0.99–1.81), $P=0.06$] compared with the normotensive group. Similarly, after additional adjustment for night-time SBP and DBP, IDH remained predictive for all cardiovascular events [hazard ratio 1.39 (95% CI 1.10–1.77), $P=0.01$], but did not predict total mortality [hazard ratio 1.03 (95% CI 0.84–1.28), $P=0.76$].

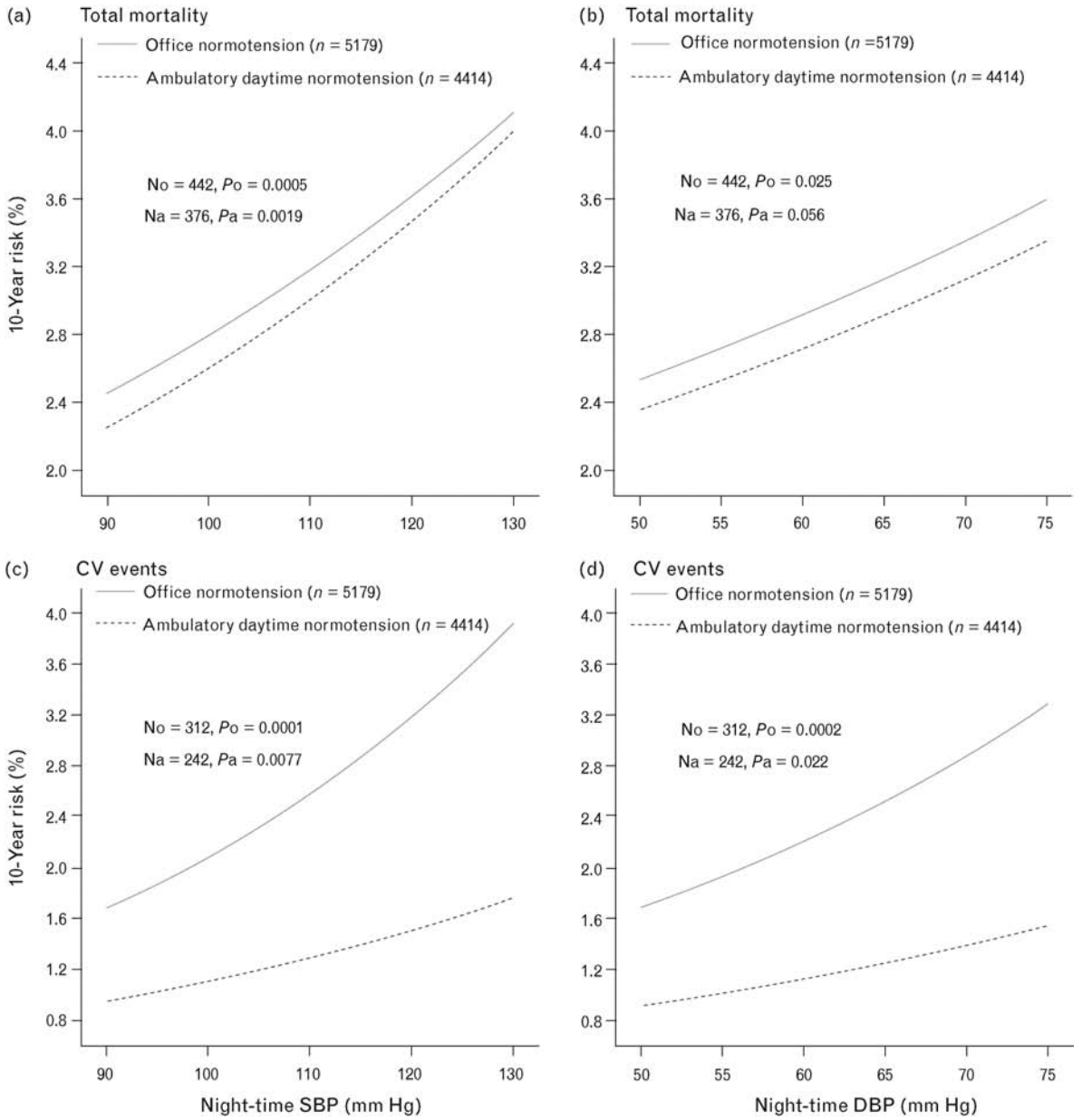
Of 8711 participants, 5179 were normotensive on office BP measurement and 4414 had daytime normotension on ambulatory BP monitoring. Figure 2 shows the continuous risk functions for total mortality and for all fatal and nonfatal cardiovascular events associated with night-time

Table 4 Adjusted hazard ratios associated with isolated nocturnal hypertension for total mortality and all cardiovascular events by baseline characteristics

	Total mortality		All cardiovascular events	
Stratification	Events/at risk	Hazard ratio (95% CI)	Events/at risk	Hazard ratio (95% CI)
All participants	1284/8711	1.29 (1.01–1.65)*	1109/8711	1.38 (1.02–1.87)*
European	830/5396	1.32 (0.96–1.82)	733/5396	1.34 (0.91–1.97)
Asian	358/1877	1.23 (0.79–1.92)	255/1877	1.37 (0.71–2.65)
South American	96/1438	0.91 (0.39–2.12)	121/1438	1.67 (0.76–3.67)
Women	411/4096	1.46 (0.93–2.29)	334/4096	1.70 (0.98–2.97)
Men	873/4615	1.21 (0.90–1.62)	775/4615	1.27 (0.88–1.83)
Age <60 years	177/4868	1.99 (1.14–3.47)*	190/4868	1.77 (0.89–3.55)
Age ≥60 years	1107/3843	1.17 (0.89–1.54)	919/3843	1.24 (0.89–1.75)
Smokers	452/2491	1.35 (0.91–2.00)	361/2491	0.80 (0.43–1.47)
Nonsmokers	832/6220	1.24 (0.90–1.71)	748/6220	1.78 (1.25–2.55)†
Drinkers	587/4126	1.13 (0.77–1.66)	531/4126	1.39 (0.89–2.19)
Nondrinkers	697/4585	1.37 (0.99–1.90)	578/4585	1.34 (0.88–2.03)
BMI <25 kg/m^2	664/4366	1.26 (0.91–1.74)	505/4366	1.63 (1.08–2.46)*
BMI ≥25 kg/m^2	620/4345	1.25 (0.85–1.84)	604/4345	1.12 (0.71–1.76)
Without CVD history	1040/7951	1.28 (0.98–1.67)	878/7951	1.27 (0.91–1.79)
With CVD history	244/760	1.57 (0.78–3.15)	231/760	2.09 (1.00–4.36)*

The hazard ratios (95% CIs) express the risk associated with isolated nocturnal hypertension relative to the normotensive group. For the covariates in the Cox models, please see the legend of Table 3. Significance of the hazard ratios: *$P<0.05$, †$P<0.01$. Heterogeneity in the risk of all cardiovascular events between smokers and nonsmokers was significant ($P=0.02$). CI, confidence interval; CVD, cardiovascular disease.

Fig. 2



Ten-year risk of total mortality (a and b) and of fatal and nonfatal combined cardiovascular events (c and d) associated with night-time SBP (left) and DBP (right) in individuals with office normotension (full lines) or with ambulatory daytime normotension (dashed lines). In Cox regression models, the incidence rates were adjusted for cohort, sex, age, BMI, smoking and drinking, serum cholesterol, history of cardiovascular disease, and diabetes mellitus. No and Na indicate the number of events in individuals with office normotension and with ambulatory daytime normotension, respectively. Po and Pa denote the corresponding significance of the independent contributions of night-time blood pressures.

SBP and DBP in individuals with office or ambulatory daytime normotension.

Of 457 patients with INH and normal office BP, 51 (11.2%) died and 38 (8.3%) experienced a composite cardiovascular endpoint. Among 120 patients with both INH and office hypertension, these numbers were 30 (25.0%) and 16 (13.3%), respectively. Although the rates were higher among patients with both INH and office hypertension compared with their counterparts with office normotension, the hazard ratios associated with INH remained significant for total mortality (1.31; 95% CI 1.01–1.68, $P = 0.039$) and for all cardiovascular events (1.38; 95% CI 1.01–1.87, $P = 0.044$) with additional adjustment for the office BP. When we considered only individuals with office normotension ($n = 5179$), the

hazard ratios associated with INH were 1.17 (95% CI 0.86–1.59, $P = 0.31$) for total mortality and 1.48 (95% CI 1.03–2.12, $P = 0.034$) for all cardiovascular events.

Discussion

The key finding of our current meta-analysis based on individual participant data was that while accounting for age, sex, and other covariables, INH was associated with a significantly higher risk of total mortality and all cardiovascular events compared with normotensive individuals. IDH predicted fatal and nonfatal cardiovascular and cardiac events. Patients with sustained hypertension carried a risk approximately twice as high for mortality and all studied cardiovascular events compared with the normotensive group. Our findings corroborated that irrespective of the type of ambulatory hypertension, an elevated BP is a major risk factor for cardiovascular complications. INH, as well as IDH, are not benign and carry a substantially increased risk versus normotension.

The unfavorable cardiovascular prognosis of INH was in keeping with our previous report on the predictive values of daytime and night-time BPs in the IDACO database, which at the time of the publication [7] consisted of 7458 individuals from six populations. When night-time and daytime BPs were analyzed as continuous variables, night-time BP predicted all mortality outcomes, and all cardiovascular, cardiac, and stroke events, independent of the daytime BP and other covariables [7]. One SD elevation of the night-time SBP and DBP increased cardiovascular risk by approximately 20%. Daytime BP did not independently predict mortality outcomes, and was only associated with cardiovascular, coronary, and stroke events [7].

Previous studies in hypertensive patients [25–29] as well as in populations [13,17,30] demonstrated that an elevated nocturnal BP or a diminished nocturnal BP fall was associated with a worse outcome. In 1542 Ohasama residents [13], each 5% decrease in the nocturnal SBP or DBP fall was associated with an approximately 20% greater risk of cardiovascular mortality. Even when 24-h BP values were within the normal range (defined as <135/80 mmHg), a diminished nocturnal BP reduction was associated with an increased risk of cardiovascular mortality. In a recently published meta-analysis [28] of individual data of 3468 hypertensive patients from four European studies, both daytime and night-time BP predicted all-cause and cardiovascular mortality, coronary heart disease, and stroke. However, when night-time and daytime BPs were added to the same Cox model, the night-time BP predicted all outcomes, whereas daytime BP did not add prognostic precision to the night-time pressure. That the night-time BP was superior to the daytime BP in the prediction of mortality outcomes was also reported in the patients randomized to placebo in the double-blind Systolic Hypertension in Europe trial [25], in Irish hypertensive patients [26], and in a recent Ohasama publication [30].

INH is a heterogeneous disorder, only characterized by an elevation of BP at night in the presence of a normal daytime BP. In the current study, 20.8% of patients with INH had office hypertension. Two other studies also reported on INH, but determined daytime normotension either by the use of office BP [3] or the self-measured BP at home [2]. The prevalence of INH was 7.2% in middle-aged patients with type 2 diabetes and close to 30% in the subgroup of diabetic patients with office normotension [3]. Irrespective of its definition, INH was associated with increased pulse wave velocity [1,3], higher central BP [3] and increased systolic augmentation [1], increased carotid intima–medial thickness, left ventricular remodeling, or all [2]. Our current results, for the first time, established the prognostic implications of INH in terms of mortality and morbidity.

The mechanisms linking INH with a worse cardiovascular outcome remain to be elucidated. Several mechanisms might be involved, such as excess sympathetic activation [31], disturbed baroreflex sensitivity or autonomic failure [32,33], decreased daytime sodium excretion [34], nocturnal pressure natriuresis [35], increased nocturnal activity [36], sleep apnea [37], insulin resistance [38], impaired endothelial function, or all [39]. Furthermore, as noticed in our current study and in previous reports [1–3], patients with INH were more likely to be older, to have diabetes, or a history of cardiovascular disease. Clustering of cardiovascular risk factors might, therefore, also contribute to the worse prognosis associated with INH.

The current study has to be interpreted within the context of its potential limitations. First, although our total sample size was over 8000, we had only 577 patients with INH and relatively few events in this group. The statistical power was low for specific cardiovascular outcomes, for instance, we had only 42 and 12% power to reject the null hypothesis of no association for cardiac events and stroke, respectively. Second, the reproducibility of INH is low. In a follow-up study [1] of the JingNing cohort, at a median interval of 3.5 years, one-third of the patients with INH at baseline kept this condition; one-third developed sustained hypertension, whereas others shifted to normotension or IDH.

Our current findings might have implications for clinical practice. INH can only be diagnosed by automated measurement of BP during sleep. Ambulatory BP monitoring is the best technique to obtain the night-time measurements in an identical way as those during daytime. Our study adds to the growing evidence that ambulatory BP monitoring should be applied more widely in clinical practice [40], and highlights the importance of having BP monitored during the whole day, rather than during a limited time window. Further studies are

needed to address the benefit of specifically lowering the night-time BP in patients with INH.

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