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Abstract—The evidence relating mortality and morbidity to heart rate remains inconsistent. We performed 24-hour ambulatory blood pressure monitoring in 6928 subjects (not on β-blockers; mean age: 56.2 years; 46.5% women) enrolled in prospective population studies in Denmark, Belgium, Japan, Sweden, Uruguay, and China. We computed standardized hazard ratios for heart rate, while stratifying for cohort, and adjusting for blood pressure and other cardiovascular risk factors. Over 9.6 years (median), 850, 325, and 493 deaths accrued for total, cardiovascular, and noncardiovascular mortality, respectively. The incidence of fatal combined with nonfatal end points was 805, 363, 439, and 324 for cardiovascular, stroke, cardiac, and coronary events, respectively. Twenty-four-hour heart rate predicted total (hazard ratio: 1.15) and noncardiovascular (hazard ratio: 1.18) mortality but not cardiovascular mortality (hazard ratio: 1.11) or any of the fatal combined with nonfatal events (hazard ratio: ≤1.02). Daytime heart rate did not predict mortality (hazard ratio: ≤1.11) or any fatal combined with nonfatal event (hazard ratio: ≤0.96). Nighttime heart rate predicted all of the mortality outcomes (hazard ratio: ≥1.15) but none of the fatal combined with nonfatal events (hazard ratio: ≤1.11). The night:day heart rate ratio predicted total (hazard ratio: 1.14) and noncardiovascular mortality (hazard ratio: 1.12) and all of the fatal combined with nonfatal events (hazard ratio: ≥1.15) with the exception of stroke (hazard ratio: 1.06). Sensitivity analyses, in which we stratified by risk factors or from which we excluded 1 cohort at a time or the events occurring within 2 years of enrollment, showed consistent results. In the general population, heart rate predicts total and noncardiovascular mortality. With the exception of the night:day heart rate ratio, heart rate did not add to the risk stratification for fatal combined with nonfatal cardiovascular events. Thus, heart rate adds little to the prediction of cardiovascular risk. (***Hypertension*. 2008;52:229-235.**)

Key Words: heart rate ■ mortality ■ cardiovascular disease ■ risk factors ■ epidemiology

Studies in hypertensive patients[1–4] or populations[5–12] suggested that heart rate, either measured at rest[1,2,4–7,9–12] or by ambulatory blood pressure monitoring,[1–3] might be a predictor of total,[1–12] cardiovascular,[4,6,7,9,11] or noncardiovascular mortality.[1,5,6] However, as highlighted by a 2006 consensus document,[13] the evidence relating outcome to heart rate remains incomplete and lacks consistency. Most researchers reported only on fatal outcomes.[3–9,11,12,14] Other investigators failed to demonstrate an independent association between total[2,14,15] or cardiovascular[1,5,15] mortality and resting[1,2,5,15] or ambulatory heart rate,[1,2,14,15] or found that adjustment for blood pressure removed the association.[8] A further issue complicating the interpretation of the published evidence is that the relation between heart rate and cardiovascular mortality or death from coronary heart disease might be more pronounced in men than in women or in middle-aged compared with older subjects.[6,7,9]

To address these issues, the 2006 consensus document[13] advocated further research. An international consortium recently constructed a database of prospective population stud-

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From the Research Center for Prevention and Health and Department of Clinical Physiology, Faculty of Health Sciences (T.W.H.), Hvidovre University Hospital, Copenhagen, Denmark; Studies Coordinating Centre (L.T., J.A.S.), Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Diseases, University of Leuven, Leuven, Belgium; Departamento de Fisiopatología (J.B.), Hospital de Clínicas, Universidad de la República, Montevideo, Uruguay; Center for Epidemiological Studies and Clinical Trials (Y.L., J.W.), Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; Tohoku University Graduate School of Pharmaceutical Science and Medicine (M.K., T.O., Y.I.), Sendai, Japan; Section of Geriatrics (K.B.-B., L.L.), Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden; Department of Epidemiology (T.R., J.A.S.), Maastricht University, Maastricht, The Netherlands; Asociación Española Primera de Socorros Mutuos (E.S.), Montevideo, Uruguay; Copenhagen University Hospital (J.J., C.T.-P.), Copenhagen, Denmark; Aarhus University and Division of Cardiology (H.I.), Holbak Hospital, Holbak, Denmark; and Conway Institute of Biomolecular and Biomedical Research (E.O.), University College Dublin, Dublin, Ireland.

Correspondence to Jan A. Staessen, Studies Coordinating Centre, Laboratory of Hypertension, University of Leuven, Campus Gasthuisberg, Herestraat 49, Box 702, B-3000 Leuven, Belgium. E-mail jan.staessen@med.kuleuven.be

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ies with the goal to advance research on the stratification of risk by ambulatory blood pressure measurement.[16,17] In keeping with the 2006 consensus document,[13] we used this international database to investigate in more detail the relation between fatal and nonfatal outcomes and heart rate on 24-hour, daytime, and nighttime measurement in >6900 subjects randomly recruited from 6 populations.

Methods

Study Population

As described in detail elsewhere,[16,17] we constructed the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes (IDACO). Studies were eligible for inclusion if they involved a random population sample, if baseline information on ambulatory blood pressure and cardiovascular risk factors was available, and if the subsequent follow-up included fatal and nonfatal outcomes.

For the current analysis, we considered 2311 residents from Copenhagen, Denmark[18]; 2542 subjects recruited from Noorderkempen, Belgium[19]; 1535 inhabitants of Ohasama, Japan[20]; 1221 older men from the population of Uppsala, Sweden[21]; 1859 subjects recruited from Montevideo, Uruguay[22]; and 360 villagers from JingNing County, China.[23] All of the studies included in IDACO received ethical approval. Participants gave informed written consent. Of the 9828 subjects, we excluded 2900 (29.6%) because they were <18 years old at the moment of enrollment (n=15), because their conventional blood pressure had not been measured (n=217), because they were on treatment with β-blockers (n=538), or because their daytime (n=224) or nighttime (n=1906) blood pressure and heart rate had not been measured or were averages of <10 or 5 readings, respectively. Thus, the number of subjects statistically analyzed totaled 6928. We also analyzed risk related to the conventional heart rate in 5742 subjects (82.9%) for whom this information was available.

Blood Pressure and Heart Rate

Trained observers measured the conventional blood pressure with a mercury sphygmomanometer[18,19,21,23] or with validated[24,25] auscultatory devices, using the appropriate cuff size, with the subjects in the sitting[18–20,22,23] or supine[21] position and counted heart rate over ≥15 seconds. The conventional blood pressure was the average of 2 consecutive readings. We defined hypertension as a conventional blood pressure of ≥140 mm Hg systolic or 90 mm Hg diastolic or as use of antihypertensive drugs. We initiated the portable blood pressure monitors to obtain blood pressure and heart rate readings at 30-minute intervals throughout the whole day[20] or at intervals ranging from 15[18] to 30[21] minutes during daytime and from 30[18] to 60[21] minutes at night.

While accounting for the daily pattern of activities of the participants, we defined daytime as the interval ranging from 10 AM to 8 PM in Europeans[18,19,21] and South Americans[22] and from 8 AM to 6 PM in Asians.[20,23] The corresponding nighttime intervals ranged from midnight to 6 AM[18,19,21,22] and from 10 PM to 4 AM,[20,23] respectively. We weighted the within-subject means of the ambulatory heart rate and blood pressure by the time interval between readings. In addition, we computed the night:day ratio of heart rate and systolic blood pressure.

Other Measurements

In all of the cohorts, we administered a questionnaire to obtain baseline information on each subject's medical history, intake of medications, and smoking and drinking habits. Body mass index was body weight in kilograms divided by height in meters squared. Serum cholesterol and blood glucose were determined by automated enzymatic methods. Diabetes mellitus was a self-reported diagnosis; a fasting or random blood glucose level of ≥7.0 mmol/L (126 mg/dL) or 11.1 mmol/L (200 mg/dL),[26] respectively; or use of antidiabetic drugs.

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.[21,27–29] Fatal and nonfatal stroke did not include transient ischemic attacks. Coronary events encompassed death from ischemic heart disease, sudden death, nonfatal myocardial infarction, and coronary revascularization. Cardiac events were composed of coronary end points and fatal and nonfatal heart failure. The composite cardiovascular end point included all of the aforementioned end points plus cardiovascular mortality. In all of the outcome analyses, we only considered the first event within each category.

Statistical Methods

For database management and statistical analysis, we used SAS 9.1.3 (SAS Institute). For comparison of means and proportions, we applied the z test for large samples and the χ^2 statistic, respectively. After stratification for cohort and sex, we imputed missing values of body mass index (n=10) and total serum cholesterol (n=48) from the regression slope on age. In subjects with unknown smoking status (n=30) or drinking habits (n=368 among Swedish men and 154 among the other cohorts), we set the design variable to the cohort- and sex-specific mean of the codes (0 and 1). Statistical significance was an α-level of 0.05 on 2-sided tests.

We used Cox regression to compute standardized hazard ratios. We checked the proportional hazards assumption by the Kolmogorov-type supremum test, as implemented in the PROC PHREG procedure of the SAS package and by testing the interaction terms between follow-up duration and the variable of interest. We first plotted incidence rates by fifths of the distributions of the daytime and nighttime heart rate while standardizing by the direct method for cohort, sex, and age (≤40, 40 to 60, and ≥60 years, respectively). We stratified Cox models for the cohort. We adjusted hazard ratios for age (treated as a continuous variable), systolic blood pressure, body mass index, smoking and drinking, serum total cholesterol, history of cardiovascular disease, diabetes mellitus, and treatment with antihypertensive drugs. Cox models, including the night:day ratio of heart rate, were additionally adjusted for the night:day ratio of systolic blood pressure. We tested heterogeneity in the hazard ratios across subgroups by introducing the appropriate interaction term in the Cox model.

Results

Baseline Characteristics

The study population consisted of 3993 Europeans (57.6%), 1553 Asians (22.4%), and 1382 South Americans (19.9%). The 6928 participants included 3219 women (46.5%) and 2494 patients with hypertension on conventional blood pressure measurement (36.0%), of whom 693 (27.8%) were taking blood pressure–lowering drugs, not including β-blockers. Mean±SD age was 56.2±14.0 years. The conventional blood pressure averaged 131.3±20.5 mm Hg systolic and 79.7±11.5 mm Hg diastolic. Heart rate averaged 72.6±9.1 bpm over 24 hours and 78.2±10.4 and 63.9±9.5 bpm during daytime and nighttime, respectively. At enrollment, 2057 participants (29.7%) were current smokers, and 3306 (47.7%) reported intake of alcohol. Conventional heart rate was available in 5742 subjects, averaging 70.4±11.6 bpm.

Table 1 shows the baseline characteristics by quartiles of the 24-hour heart rate. Across the quartiles, all of the characteristics were significantly different ($P<0.05$), with the exception for 24-hour systolic blood pressure ($P=0.68$), nighttime systolic blood pressure ($P=0.33$), and the proportion of patients with diabetes mellitus ($P=0.70$) or a history of cardiovascular disease ($P=0.78$). Participants with a

Table 1. Baseline Characteristics of Participants by Quartiles of 24-Hour Heart Rate

Characteristic	Quartiles of 24-h Heart Rate			
Limits, bpm	≤66.3	>66.3 to ≤72.2	>72.2 to ≤78.4	>78.4
All subjects in category, n (%)	n=1732	n=1732	n=1732	n=1732
European	1083 (62.5)	1008 (58.2)	980 (56.6)	922 (53.2)
Asian	592 (30.5)	484 (27.9)	361 (20.8)	179 (10.3)
South American	120 (6.9)	240 (13.9)	391 (22.6)	631 (36.4)
Women	580 (33.5)	811 (46.8)	883 (51.0)	945 (54.6)
Antihypertensive treatment*	351 (20.3)	264 (15.3)	149 (14.4)	236 (13.6)
Smokers	366 (21.2)	454 (26.4)	563 (32.6)	674 (39.0)
Using alcohol	875 (57.7)	834 (52.2)	883 (50.8)	764 (46.3)
Diabetes mellitus	122 (7.0)	124 (7.2)	113 (6.5)	109 (6.3)
Cardiovascular disorder	125 (7.2)	124 (7.2)	112 (6.5)	125 (7.2)
Age, mean±SD, y	60.2±13.2	57.5±13.0	55.1±13.9	51.8±14.2
Body mass index, mean±SD, kg/m^2	25.1±3.6	25.3±3.9	25.5±4.1	26.0±4.7
Conventional heart rate, mean±SD, bpm†	61.2±8.6	67.0±8.1	71.9±8.9	79.5±11.4
Ambulatory measurements, mean±SD				
Daytime heart rate, bpm	66.1±5.4	75.0±3.9	81.1±4.2	90.7±6.8
Nighttime heart rate, bpm	54.2±5.1	60.7±4.8	66.1±5.2	74.6±7.9
24-h systolic, mm Hg	125.2±13.8	124.5±14.5	124.2±14.3	123.7±15.0
24-h diastolic, mm Hg	72.1±7.8	73.2±8.4	74.4±8.2	75.9±9.1
Daytime systolic, mm Hg	131.7±14.8	131.3±15.8	130.7±15.3	130.0±15.9
Daytime diastolic, mm Hg	76.8±8.6	78.2±9.1	79.6±9.2	81.2±9.8
Nighttime systolic, mm Hg	113.8±15.0	112.6±14.9	112.4±15.2	112.3±16.0
Nighttime diastolic, mm Hg	63.8±8.6	64.4±9.1	65.1±8.7	66.3±10.1
Serum cholesterol, mmol/L	5.6±1.1	5.7±1.2	5.7±1.1	5.8±1.2

Trend tests across the 4 groups were significant ($P<0.05$) except for 24-hour systolic blood pressure ($P=0.68$), nighttime systolic blood pressure ($P=0.33$), and the prevalence of diabetes mellitus ($P=0.70$) and cardiovascular disorder ($P=0.78$).

*Subjects treated with β-blockers were excluded.

†Data were available in 5742 subjects.

higher heart rate were younger and more likely to be female and smokers compared with those with lower heart rate (Table 1).

Incidence of Events

In the overall study population, the median follow-up was 9.6 years (fifth to 95th percentile interval: 2.5 to 13.8 years). Across cohorts, median follow-up ranged from 2.5 years (fifth to 95th percentile interval: 2.3 to 2.6 years) in JingNing to 13.2 years (fifth to 95th percentile interval: 0.9 to 15.8 years) in Noorderkempen. During 64 400 person-years of follow-up, 850 participants died (13.2 per 1000 person-years), and 805 experienced a fatal or nonfatal cardiovascular complication (13.0 per 1000 person-years). Mortality included 325 cardiovascular and 493 noncardiovascular deaths and 32 deaths from unknown cause (Table 2). Considering cause-specific first cardiovascular events, the incidence of fatal and nonfatal stroke amounted to 49 and 314, respectively. Cardiac events consisted of 116 fatal and 323 nonfatal events, including 57 fatal and 157 nonfatal cases of acute myocardial infarction, 19 deaths from ischemic heart diseases, 24 sudden deaths, 16 fatal and 121 nonfatal cases of heart failure, and 45 cases of surgical or percutaneous coronary revascularization. Of the coronary revascularization procedures, 16 occurred in Noorderkempen, 1 in Copenhagen, and 28 in Montevideo.

Risk Associated With Heart Rate and Blood Pressure

The Figure shows the cohort-, sex-, and age-standardized rates of mortality and fatal combined with nonfatal outcomes across quintiles of the daytime and nighttime heart rates. The multivariate-adjusted hazard ratios associated with 1-SD increase in the conventional and ambulatory heart rates appear in Table 2 for fatal end points, as well as for fatal combined with nonfatal cardiovascular events.

Mortality

In adjusted models, nighttime heart rate predicted total, cardiovascular, and noncardiovascular mortality, whereas daytime heart rate did not predict any of these fatal outcomes. The conventional heart rate, the 24-hour heart rate, and the night:day ratio of heart rate predicted total and noncardiovascular mortality but not death from cardiovascular causes (Table 2). The figure in the data supplement, available online at http://hyper.ahajournals.org, shows the absolute risk of total and noncardiovascular mortality in relation to the nighttime heart rate at different levels of 24-hour systolic

Table 2. Adjusted Standardized Hazard Ratios Relating Heart Rate to Different Outcomes

	Mortality			Combined Cardiovascular Outcomes			
Label	Total	Cardiovascular	Noncardiovascular	All	Stroke	Cardiac	Coronary
Events, n (%)	697 (12.1)	277 (4.8)	389 (6.8)	693 (12.1)	269 (4.7)	426 (7.4)	313 (5.5)
Conventional	1.14 (1.04 to 1.25)†	1.14 (0.99 to 1.32)	1.17 (1.03 to 1.32)*	1.03 (0.94 to 1.12)	0.94 (0.81 to 1.09)	1.06 (0.95 to 1.19)	1.07 (0.94 to 1.22)
Events, n (%)	850 (12.3)	325 (4.7)	493 (7.1)	805 (11.6)	363 (5.2)	439 (6.3)	324 (5.7)
24-h	1.15 (1.06 to 1.25)‡	1.11 (0.97 to 1.26)	1.18 (1.06 to 1.31)‡	0.99 (0.91 to 1.07)	0.93 (0.82 to 1.06)	1.00 (0.90 to 1.12)	1.02 (0.90 to 1.16)
Daytime	1.08 (0.99 to 1.16)	1.05 (0.92 to 1.19)	1.11 (1.00 to 1.23)	0.94 (0.87 to 1.02)	0.91 (0.81 to 1.03)	0.93 (0.84 to 1.04)	0.96 (0.85 to 1.09)
Nighttime	1.20 (1.11 to 1.30)‡	1.15 (1.01 to 1.31)*	1.22 (1.10 to 1.36)‡	1.06 (0.97 to 1.15)	0.96 (0.84 to 1.09)	1.11 (1.00 to 1.24)	1.10 (0.97 to 1.25)
Night:day ratio	1.14 (1.05 to 1.23)‡	1.12 (0.99 to 1.27)	1.12 (1.01 to 1.24)*	1.15 (1.06 to 1.24)‡	1.06 (0.94 to 1.19)	1.23 (1.10 to 1.35)‡	1.17 (1.04 to 1.31)†

Values are standardized hazard ratios (95% CIs), which express the risk per SD increase in the heart rate, unless otherwise specified. Heart rate SDs were 11.6, 9.1, 10.4, and 9.5 bpm for conventional, 24-hour, daytime, and nighttime, respectively. The SD of night:day heart rate ratio was 0.09. The cause of death was unknown in 32 cases. Conventional heart rate was available in 5742 subjects. All of the hazard ratios were stratified by cohort and adjusted for age, systolic blood pressure measured over the same interval as heart rate, body mass index, smoking and drinking, serum total cholesterol, history of cardiovascular disease, diabetes mellitus, and treatment with antihypertensive drugs. The analyses of the night:day ratio of heart rate were additionally adjusted for night:day ratio of systolic blood pressure.

Significance of the hazard ratios: *$P<0.05$, †$P<0.01$, and ‡$P<0.001$.

blood pressure, while stratifying for cohort and adjusting for covariates.

Fatal and Nonfatal Cardiovascular Events

With adjustments applied as before (Table 2), the night:day ratio of heart rate ($P<0.005$) predicted cardiovascular, as well as cardiac and coronary, events but not fatal and nonfatal stroke ($P=0.23$). However, heart rate did not predict ($P\geq0.06$) any of the fatal combined with nonfatal outcomes, irrespective of whether it was measured in the clinic, over 24 hours, or over daytime or nighttime (Table 2).

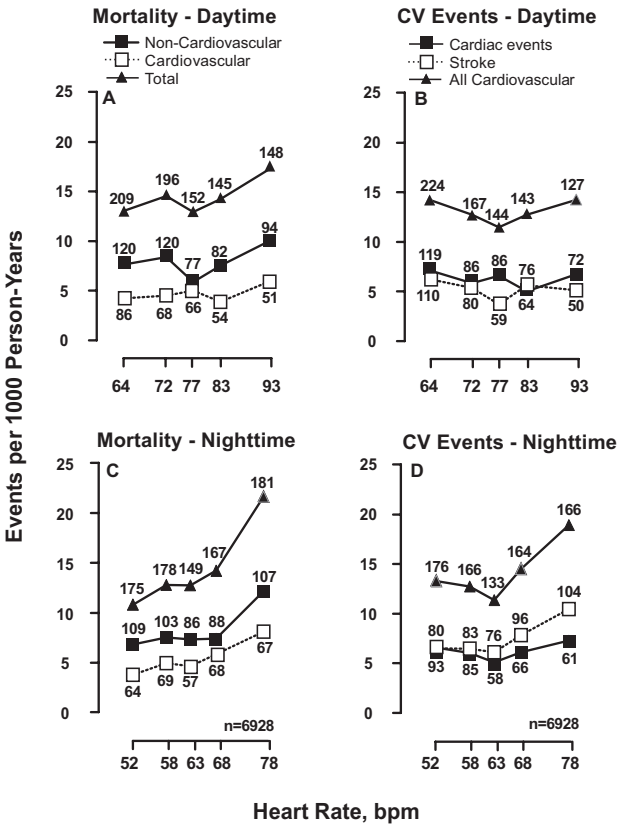

Figure. Incidence of mortality (A and C) and cardiovascular events (B and D) by fifths of the distributions of the daytime (A and B) and nighttime (C and D) heart rate in 6928 participants. Incidence rates were standardized for cohort, sex, and age by the direct method. The number of events contributing to the rates is presented.

Sensitivity Analyses

In sensitivity analyses, we considered total and noncardiovascular mortality in relation to the 24-hour and nighttime heart rate and to the night:day ratio of heart rate. We stratified the study population according to sex, median age (60 years), history of cardiovascular disease, smoking and drinking habits, treatment status, and the presence or absence of hypertension on conventional blood pressure measurement. Table 3 lists the characteristics, for which we noticed a significant difference between the strata for ≥1 outcome. For all of the other stratification factors, the interaction terms with the 24-hour ($P\geq0.06$) or nighttime ($P\geq0.13$) heart rate or with the night:day ratio of heart rate ($P\geq0.13$) were not statistically significant. Furthermore, sensitivity analyses from which we excluded 1 cohort at a time produced results consistent with those in the overall study population (Table S1). Moreover, the addition of an interaction term between ethnicity (Asian, Latin American, or European) and any measure of heart rate did not improve the fit of the Cox models ($P\geq0.09$).

Calcium channel blockers can influence heart rate. A sensitivity analysis from which we excluded patients treated with β-blockers, calcium channel blockers, or both produced consistent results (Table S2). The prevalence of a history of cardiovascular disease was 6.8% and 26.0% in participants not or on β-blockade at enrollment ($P<0.001$). However, including 538 patients on β-blockers did not materially alter our results (Table S3).

Finally, our results remained consistent when we analyzed ambulated heart rate standardized to a body height of 165 cm (median of the whole study population), when we added a squared term of ambulated heart rate to the regression models, when we substituted systolic blood pressure in our models by diastolic blood pressure or mean arterial pressure, or when we added conventional heart rate to models already including ambulatory heart rate. Our results also did not

Table 3. Adjusted Standardized Hazard Ratios Relating Heart Rate to Different Outcomes According to Baseline Characteristics

Stratification	At Risk, n	Events, n	24-h, Hazard Ratio (95% CI)	Nighttime, Hazard Ratio (95% CI)	Night:Day Ratio, Hazard Ratio (95% CI)
Total mortality					
All participants	6928	850	1.15 (1.06 to 1.25)‡	1.20 (1.11 to 1.30)‡	1.14 (1.05 to 1.23)‡
<60 y	3636	113	1.20 (0.96 to 1.49)	1.41 (1.15 to 1.72)‡ } 0.03	1.39 (1.15 to 1.65)‡
≥60 y	3292	737	1.14 (1.05 to 1.24)‡	1.17 (1.07 to 1.28)‡	1.09 (1.00 to 1.19)*
Normotensive	4434	397	1.17 (1.03 to 1.32)†	1.28 (1.13 to 1.44)‡	1.25 (1.11 to 1.40)‡ } 0.02
Hypertensive	2494	453	1.15 (1.03 to 1.28)†	1.15 (1.03 to 1.29)†	1.05 (0.94 to 1.16)
Noncardiovascular mortality					
All participants	6928	493	1.18 (1.06 to 1.31)‡	1.22 (1.10 to 1.356)‡	1.12 (1.01 to 1.24)*
Women	3219	139	0.98 (0.80 to 1.20) } 0.04	1.08 (0.89 to 1.32)	1.08 (0.96 to 1.23)
Men	3709	354	1.27 (1.12 to 1.44)‡	1.29 (1.14 to 1.46)‡	1.24 (1.02 to 1.50)*
<60 y	3636	74	1.20 (0.92 to 1.58)	1.40 (1.09 to 1.79)*	1.36 (1.09 to 1.70)‡ } 0.01
≥60 y	3292	419	1.17 (1.04 to 1.32)†	1.18 (1.05 to 1.33)†	1.06 (0.94 to 1.20)

Hypertension was a conventional blood pressure of ≥140 mm Hg systolic or 90 mm Hg diastolic or the use of antihypertensive drugs. All of the hazard ratios were stratified by cohort and adjusted for age, systolic blood pressure measured over the same interval as heart rate, body mass index, smoking and drinking, serum total cholesterol, history of cardiovascular disease, diabetes mellitus, and treatment with antihypertensive drugs. The analyses of the night:day ratio of heart rate were additionally adjusted for night:day ratio of systolic blood pressure. Braces point to heterogeneity between subgroups (*P* value given).

Significance of the hazard ratios: **P*<0.05, †*P*<0.01, and ‡*P*<0.001.

change when we excluded subjects who experienced an event within 2 years of enrollment (Table S4).

Discussion

The key finding of our study was that a higher heart rate significantly and independently predicted total mortality. This effect was mainly mediated by the association of heart rate with noncardiovascular mortality rather than cardiovascular mortality. Nighttime heart rate predicted cardiovascular mortality with a 14% higher risk per SD increase in the cardiac frequency (≈10 bpm). Neither daytime nor nighttime heart rate predicted any of the fatal combined with nonfatal cardiovascular end points. The night:day ratio of heart rate contributed to the overall cardiovascular risk and fatal combined with nonfatal cardiac and coronary events. In the interpretation of our results, one should consider that we implemented an analysis on the basis of data from individual participants. In terms of standardization and quality, such an approach is better than undertaking a meta-analysis of aggregate data extracted from publications.[30]

Most studies relating health outcomes to heart rate used office measurement of the cardiac frequency.[1,2,4–7,9–12] Ambulatory heart rate, as recorded in our current study, compared with counting the heart rate in the office, has higher reproducibility,[31] is not subject to observer bias, is less prone to measurement error, and avoids the transient rise of a patient's heart rate by arousal in response to a medical environment.[13,32] By and large, our present results are in line with those of other researchers, who used ambulatory[1–3,14,33] rather than office measurement of the heart interval.[1,2,4–7,9–12]

In the Systolic Hypertension in Europe Trial,[1] in which ambulatory heart rate was recorded during the run-in period in 807 untreated patients, none of the ambulatory heart rate measurements predicted nonfatal events or nonfatal combined with fatal end points, respectively.[1] Verdecchia et al[2] studied 1942 hypertensive patients enrolled in the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale. The 24-hour heart rate was unrelated to total mortality or combined fatal and nonfatal cardiovascular events. However, in analyses adjusted for blood pressure and other risk factors, each 10% decrease in the nocturnal slowing of heart rate was associated with higher total mortality (hazard ratio: 1.30; 95% CI: 1.02 to 1.65) but not with cardiovascular events.[2] Ben-Dov et al[3] analyzed total mortality in 3957 referred patients across deciles of the awake and asleep heart rate and of the nocturnal decrease in heart rate. He demonstrated that total mortality increased with higher sleeping heart rate ($P=0.02$) and decreased with more nocturnal fall in heart rate ($P<0.001$) but was unrelated to the awake heart rate ($P=0.50$). Two population studies, the Ohasama Study[14] and the Pressioni Arteriose Monitorate e Loro Associazioni Study,[15] reported on the association of total[14,15] or cardiovascular[15] mortality with heart rate. The Japanese researchers failed to detect any association of cardiovascular mortality with 24-hour, daytime, or nighttime heart rate.[14] The Pressioni Arteriose Monitorate e Loro Associazioni findings were equally negative for both total and cardiovascular mortality.[15] In contrast, home heart rate was a significant predictor of cardiovascular mortality in 1780 Japanese subjects included in the Ohasama Study.[34]

The present study has potential limitations. First, the IDACO database is currently composed of 6 population-based cohorts from 3 continents,[18–23] but our results might not yet be generally applicable, in particular to Africans of black ancestry or African Americans. For this reason, we are presently collecting outcome results in additional cohorts, although to our knowledge no prospective population data are available in black subjects.[35–37] Second, the 6 populations differed in anthropometric characteristics and lifestyle, and conventional heart rate was only available in 82.9% of our

study population. Sensitivity analyses showed that no single cohort had a disproportionately large influence. Moreover, a very recent analysis of the Ohasama cohort with follow-up of mortality extended to a median of 12 years (296 deaths) confirmed that, even in the long run, higher nighttime heart rate predicted total mortality.[38] Third, we and most other investigators[2–5,7,9,14,15] did not adjust for important determinants of heart rate, such as hemoglobin concentration, hematocrit, or usual physical activity. In particular, low hemoglobin is an index of poor health, is associated with a higher heart rate,[32] and might be a forerunner of imminent cardiovascular or noncardiovascular events. However, our results remained consistent if we excluded patients with an event within 2 years of enrollment. Smoking and drinking alcohol influence heart rate, but our findings were consistent across these strata. Finally, observational data, even if prospective, only allow us to speculate why heart rate is a predictor of total and noncardiovascular mortality. The night:day ratios of heart rate and blood pressure are associated. We demonstrated previously that reverse causality might explain why less nocturnal blood pressure dipping might predict outcome.[17] Subjects in bad health with low mobility are more likely to have an attenuated diurnal rhythm of both blood pressure and heart rate.

Within the limitations of our study, our current findings challenge the commonly held point of view, echoed in recent hypertension guidelines,[39,40] that heart rate must be a predictor of cardiovascular complications. The 2007 guideline of the joint European Societies of Cardiology and Hypertension[39] stated that there might be reasons to include an elevated heart rate as a risk factor because of the growing body of evidence that higher heart might be related to cardiovascular morbidity and mortality, as well as to all-cause mortality. The 3 references to substantiate this recommendation[1,5,6] included studies with null findings on the association of heart rate with cardiovascular mortality[1,5] and no study with positive findings for the association with cardiovascular morbidity. In fact, only the Atherosclerosis Risk in Communities studies[10] demonstrated a positive association between coronary heart disease and office heart rate but only limited to women in analyses without adjustment for blood pressure.[10] The Joint National Committee guideline, version 7,[40] stated that data from epidemiological studies and clinical trials have demonstrated that elevations in resting heart rate[4] and reduced heart rate variability[41] were associated with higher cardiovascular risk. This statement was mainly based on the Framingham Heart Study,[4,5] in which an average resting heart rate of 83 bpm, according to the expert committee,[40] was associated with a substantially higher risk of cardiovascular mortality. However, Kannel et al[5] reported that there was a substantial excess of noncardiovascular deaths at higher heart rates but that the proportion of cardiovascular deaths did not increase with heart rate.

Perspectives

In the general population, heart rate predicts total and noncardiovascular mortality. With the exception of the night:day ratio, heart rate does not significantly add to the risk stratification for fatal combined with nonfatal cardiovascular events. Additional studies must clarify to what extent previously published results reflect publication bias, studies with positive results being more likely to be published, or might be influenced by red blood cell volume as a harbinger of events or by the level of usual physical activity. To our knowledge, only the findings from Systolic Hypertension in Europe Trial[1] and the Cardiovascular Occupational Risk Factors Detection in Israeli Industries Study[11] were adjusted for hemoglobin. Only 4 studies[6,8,10,11] accounted for physical activity. Expert committees might have to reassess the evidence on which current hypertension guidelines[39,40] propose heart rate as a consistent predictor of risk.

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Disclosures

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