Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study

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Summary

Background Few studies have formally compared the predictive value of the blood pressure at night over and beyond the daytime value. We investigated the prognostic significance of the ambulatory blood pressure during night and day and of the night-to-day blood pressure ratio.

Methods We did 24-h blood pressure monitoring in 7458 people (mean age 56·8 years [SD 13·9]) enrolled in prospective population studies in Denmark, Belgium, Japan, Sweden, Uruguay, and China. We calculated multivariate-adjusted hazard ratios for daytime and night-time blood pressure and the systolic night-to-day ratio, while adjusting for cohort and cardiovascular risk factors.

Findings Median follow-up was 9·6 years (5th to 95th percentile 2·5–13·7). Adjusted for daytime blood pressure, night-time blood pressure predicted total (n=983; p<0·0001), cardiovascular (n=387; p<0·01), and non-cardiovascular (n=560; p<0·001) mortality. Conversely, adjusted for night-time blood pressure, daytime blood pressure predicted only non-cardiovascular mortality (p<0·05), with lower blood pressure levels being associated with increased risk. Both daytime and night-time blood pressure consistently predicted all cardiovascular events (n=943; p<0·05) and stroke (n=420; p<0·01). Adjusted for night-time blood pressure, daytime blood pressure lost prognostic significance only for cardiac events (n=525; p≥0·07). Adjusted for the 24-h blood pressure, night-to-day ratio predicted mortality, but not fatal combined with non-fatal events. Antihypertensive drug treatment removed the significant association between cardiovascular events and the daytime blood pressure. Participants with systolic night-to-day ratio value of 1 or more were older, at higher risk of death, and died at an older age than those whose night-to-day ratio was normal (≥0·80 to <0·90).

Interpretation In contrast to commonly held views, daytime blood pressure adjusted for night-time blood pressure predicts fatal combined with non-fatal cardiovascular events, except in treated patients, in whom antihypertensive drugs might reduce blood pressure during the day, but not at night. The increased mortality in patients with higher night-time than daytime blood pressure probably indicates reverse causality. Our findings support recording the ambulatory blood pressure during the whole day.

Introduction

In 1988, O'Brien and colleagues[1] reported for the first time that an abnormal circadian blood-pressure profile with a less marked decrease in night-time blood pressure led to an increased risk of stroke. Subsequent studies of populations[2–5] and hypertensive cohorts[6–12] generally corroborated that a raised nocturnal blood pressure predicted a higher rate of cardiovascular complications. Despite the apparent agreement between these previously published large-scale studies,[2–12] several potential limitations need further clarification of the prognostic accuracy of day versus night ambulatory blood pressure. Many studies considered only fatal outcomes[2,3,10,11] or did not have the power to study cause-specific cardiovascular endpoints.[2,3,5,9] Investigators dichotomised the night-to-day blood pressure ratio, and applied different definitions of dipping status or different daytime and night-time intervals. Few reports formally compared the predictive value of the blood pressure at night over and beyond the daytime value. Finally, in cohorts of patients with hypertension,

antihypertensive drug treatment attenuated the association between outcome and blood pressure.[7]

An international consortium constructed a database of prospective population studies with the goal to advance research on the prognostic accuracy of the ambulatory blood pressure.[13,14] We aimed to report risk estimates that were independently associated with the daytime and night-time blood pressures. Additionally, we investigated in categorical and continuous analyses whether the night-to-day blood pressure ratio contained any prognostic information over and beyond the 24-h blood pressure.

Methods

Study population

We constructed the International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO).[13,14] Studies were eligible for inclusion if they included a random population sample, if information about the conventional and ambulatory blood pressures and cardiovascular risk

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factors were available at baseline, and if the subsequent follow-up included fatal and non-fatal outcomes. We did an electronic search of studies written in English, using the search terms "ambulatory blood pressure monitoring" and "population", which identified 11 studies.[2–5,15–21] We excluded five because at the time of writing they were still in progress[15,18,21] or had not yet been organised,[20] or because follow-up did not include non-fatal events.[5]

For our analysis, we included 2311 residents from Copenhagen, Denmark;[3] 2542 from Noorderkempen, Belgium;[16] 1535 from Ohasama, Japan;[2] 1859 from Montevideo, Uruguay;[19] 360 from the JingNing county, China;[17] and 1221 70-year-old men from Uppsala, Sweden.[4] All studies included in IDACO received ethical approval[2–4,16,17,19] and have previously been described in detail.[2–4,16,17,19] All participants provided informed written consent. Of the 9828 participants, we excluded 2370 (24%), because they were younger than 18 years old at enrolment (n=15), because their conventional blood pressure had not been measured (n=217), or because their daytime (n=229) or night-time (n=1909) blood pressure had not been registered or were averages of fewer than ten daytime or five night-time readings. Thus, 7458 people were included in the analysis.

	Extreme	Normal	Decreased	Reverse
Limits	<0·80	≥0·80 to <0·90	≥0·90 to <1·00	≥1·00
Total	1513	3754	1754	437
European	987 (65%)†	2299 (61%)	894 (51%)§	178 (41%)§
Asian	317 (21%)	776 (21%)	433 (24%)‡	140 (32%)§
South American	209 (14%)‡	679 (18%)	427 (24%)§	119 (27%)§
Women	670 (44%)	1728 (46%)	832 (47%)	186 (43%)
Antihypertensive treatment	336 (22%)†	698 (19%)	440 (25%)§	163 (37%)§
Smokers	456 (30%)	1150 (31%)	455 (26%)‡	111 (25%)*
Alcohol drinkers	809 (54%)‡	1812 (48%)	755 (43%)‡	164 (38%)§
Diabetes mellitus	99 (7%)	259 (7%)	131 (8%)	54 (12%) §
Cardiovascular disorder	138 (9%)*	273 (7%)	155 (9%)*	60 (14%)§
Age (years)	58·6 (12·5)§	55·2 (13·8)	57·1 (14·5)§	62·9 (14·0)§
Body-mass index (kg/m²)	25·6 (4·0)	25·5 (4·0)	25·6 (4·4)	25·4 (4·7)
Conventional blood pressure (mm Hg)				
Systolic	134·0 (19·4)§	131·1 (20·6)	132·7 (21·8)†	136·5 (22·5)§
Diastolic	80·9 (10·9)†	79·9 (11·6)	79·7 (12·1)	79·4 (12·3)
Ambulatory blood pressure (mm Hg)				
24-h systolic	124·8 (12·6)†	123·7 (14·1)	125·6 (15·5)§	131·0 (17·9)§
24-h diastolic	73·7 (7·6)	73·7 (8·4)	74·6 (9·2)‡	75·4 (9·7)§
Night-time systolic	104·0 (10·7)§	111·1 (12·9)	120·2 (15·1)§	134·8 (19·8)§
Night-time diastolic	60·1 (6·9)§	64·1 (8·2)	68·9 (9·5)§	74·1 (10·8)§
Daytime systolic	137·3 (14·4)§	130·7 (15·0)	128·1 (15·8)§	126·8 (16·7)§
Daytime diastolic	81·7 (8·8)§	79·0 (9·0)	77·4 (9·6)§	75·3 (10·1)§
Serum cholesterol (mmol/L)	5·82 (1·15)†	5·72 (1·13)	5·64 (1·14)*	5·48 (1·12)§

Data are number (%) or mean (SD). p values for the differences with normal: *p<0·05, †p<0·01, ‡p<0·001, §p<0·0001.

Table 1: Baseline characteristics of participants by categories of the night-to-day ratio of systolic blood pressure

Procedures

Trained observers measured the conventional blood pressure with a mercury sphygmomanometer[3,4,16,17] or with validated auscultatory[22,23] (USM-700F, UEDA Electronic Works, Tokyo, Japan)[2] or oscillometric (OMRON HEM-705CP, Omron Corporation, Tokyo, Japan)[19] devices, using the appropriate cuff size, with participants in the sitting[2,3,16,17,19] or supine[4] position. Conventional blood pressure was the average of two consecutive readings obtained either at the persons' home[16,17,19] or at an examination centre.[2–4] We defined hypertension as a conventional blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic, or as use of antihypertensive drugs.

We initiated portable blood-pressure monitors to obtain readings every 30-min throughout the whole day[2] or at intervals ranging from 15 min[3] to 30 min[4] during daytime, and from 30 min[3] to 60 min[4] at night. The devices implemented an auscultatory algorithm (Accutracker II, Suntech Medical Instruments Inc, Morrisville, USA[24]) in Uppsala[4] or an oscillometric technique (SpaceLabs 90202 and 90207, SpaceLabs Inc, Redmond, USA[25]) in Noorderkempen,[16] Montevideo,[19] and JingNing.[17] The Takeda TM-2421 recorders (A&D, Tokyo, Japan[26]) used in Copenhagen[3] and the ABPM-630 devices (Nippon Colin, Komaki, Japan[27]) used in Ohasama[2] implemented both techniques, but we only analysed the oscillometric readings.

The same SAS macro processed all ambulatory recordings, which generally stayed unedited. The Ohasama recordings were edited sparsely according to previously published criteria.[28] When accounting for the daily pattern of activities of the participants, we defined daytime as the interval ranging from 1000 h to 2000 h in people from Europe[3,4,16] and South America,[19] and from 0800 h to 1800 h in those from Asia.[2,17] The corresponding night-time intervals ranged from midnight to 0600 h[3,4,16,19] and from 2200 h to 0400 h.[2,17] These fixed intervals eliminate the transition periods in the morning and evening when blood pressure changes rapidly, resulting in daytime and night-time blood pressure levels that are within 1–2 mm Hg of the awake and asleep levels.[17,29] We weighted the individual means of the ambulatory blood pressure by the interval between readings.

In categorical analyses, we classified the participants according to the night-to-day ratio of systolic blood pressure because mean age was 56·8 years and in adults older than 50 years systolic rather than diastolic blood pressure is the predominant risk factor.[30] Moreover, we previously showed that the systolic night-to-day ratio, but not the diastolic night-to-day ratio, was similar in auscultatory and oscillometric recordings.[31] We also avoided divergent classification of participants on the basis of systolic or diastolic blood pressure or both, using the systolic night-to-day ratio. Normal dipping, used as the reference group in categorical analyses, was a night-to-day ratio ranging from less than 0·90 to 0·80 inclusive. We

labelled the other categories of dipping status as extreme (<0·80),[8] decreased (≥0·90–<1·00), and reverse (≥1·00).[8]

In all cohorts, we administered a questionnaire to obtain baseline information about every participant's medical history, intake of drugs, and smoking and drinking habits. Body-mass index was body weight (kg) divided by height (m) squared. Serum cholesterol and blood glucose concentrations were recorded by automated enzymatic methods. Diabetes mellitus was a self-reported diagnosis, or a fasting blood glucose concentration of at least 7·0 mmol/L or a random blood glucose concentration of 11·1 mmol/L,[32] or use of antidiabetic drugs.

We ascertained vital status and incidence of fatal and non-fatal diseases from the appropriate sources in every country, as described in detail in previous publications.[4,33–35] Fatal and non-fatal stroke did not include transient ischaemic attacks. Coronary events encompassed death from ischaemic heart disease, sudden death, non-fatal myocardial infarction, and coronary revascularisation. Cardiac events consisted of coronary endpoints and fatal and non-fatal heart failure. In the Swedish cohort, the diagnosis of heart failure required admission to hospital. In the other cohorts,[17,19,33–35] heart failure was either a clinical diagnosis or the diagnosis on the death certificate, but all cases were validated against hospital files or the records held by family doctors. The composite cardiovascular endpoint included all these endpoints plus cardiovascular mortality. In all outcome analyses we considered only the first event within every category.

Statistical analysis

For database management and statistical analysis, we used SAS software (version 9.1.3; SAS Institute, Cary NC, USA). For comparison of means we applied the Z test for large samples and for comparison of proportions we applied the χ^2-statistic. After stratification for cohort and sex, we interpolated missing values of body-mass index (n=10) and total serum cholesterol (n=52) from the regression slope on age. In participants with unknown drinking (n=34) or smoking habits (n=445 in Swedish men[4] and 167 in other cohorts[17,19,33–35]), we set the design variable to the cohort-specific and sex-specific mean of the codes (0,1). Statistical significance was an α-level of 0·05 on two-sided tests.

We used Cox regression to compute standardised 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 either blood pressure or the night-to-day blood pressure ratio. We first plotted incidence rates by quintiles of the blood pressure distributions, while standardising by the direct method for cohort, sex, and age (≤40, 40–60, and ≥60 years). In adjusted models, we treated age as a continuous variable

	Total	Non-cardiovascular	Cardiovascular
Number of deaths (%)	983 (13%)	560 (8%)	387 (5%)
Daytime blood pressure			
Systolic			
Adjusted	1·09 (1·02–1·16)*	0·96 (0·88–1·05)	1·29 (1·17–1·42)§
Fully adjusted	0·94 (0·87–1·03)	0·84 (0·75–0·94)†	1·11 (0·98–1·27)
Diastolic			
Adjusted	1·06 (0·99–1·14)	0·97 (0·89–1·06)	1·24 (1·12–1·37)§
Fully adjusted	0·94 (0·87–1·03)	0·88 (0·79–0·98)*	1·07 (0·94–1·22)
Night-time blood pressure			
Systolic			
Adjusted	1·18 (1·11–1·25)§	1·10 (1·01–1·19)*	1·29 (1·19–1·41)§
Fully adjusted	1·22 (1·13–1·31)§	1·21 (1·10–1·33)‡	1·22 (1·09–1·36)‡
Diastolic			
Adjusted	1·16 (1·09–1·24)§	1·09 (1·00–1·19)*	1·29 (1·18–1·42)§
Fully adjusted	1·20 (1·11–1·30)§	1·18 (1·06–1·31)†	1·24 (1·10–1·40)‡
Night-to-day blood pressure ratio			
Systolic			
Adjusted	1·15 (1·09–1·21)§	1·16 (1·08–1·24)§	1·13 (1·04–1·23)†
Fully adjusted	1·13 (1·07–1·19)§	1·16 (1·08–1·25)§	1·08 (0·99–1·17)
Diastolic			
Adjusted	1·13 (1·07–1·20)§	1·14 (1·05–1·23)†	1·13 (1·03–1·24)†
Fully adjusted	1·12 (1·06–1·19)‡	1·14 (1·05–1·23)†	1·10 (1·00–1·21)*

Data are number (%) or standardised hazard ratios (95% CI), which express the risk per SD increase in the blood-pressure variables. Systolic/diastolic SDs were 15·52/9·33 mm Hg and 15·53/9·25 mm Hg for the day and night blood pressures and 0·08/0·09 for the night-to-day blood pressure ratio. The cause of death was unknown in 36 cases. All hazard ratios were adjusted for cohort, sex, age, body-mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, and antihypertensive drug treatment. In fully adjusted models, the daytime blood pressure was additionally adjusted for the night-time blood pressure (and vice versa), and the night-to-day ratio was additionally adjusted for the 24-h blood pressure. *p<0·05. †p<0·01. ‡p<0·001. §p<0·0001.

Table 2: **Adjusted standardised hazard ratios for mortality**

and additionally accounted for body-mass index, smoking and drinking, serum total cholesterol, history of cardiovascular disease, diabetes mellitus, and treatment with antihypertensive drugs. Fully adjusted models for the daytime blood pressure additionally included the corresponding night-time blood pressure, and vice versa, and for the night-to-day ratio they additionally included the 24-h systolic blood pressure. We adjusted for cohort by introducing five design variables in the Cox models. We analysed the night-to-day blood pressure ratios both as continuous and categorical variables. In the categorical analyses, we plotted Kaplan-Meier survival function estimates according to present recommendations.[36] We tested heterogeneity in the hazard ratios across subgroups by introduction of the appropriate interaction term in the Cox model.

Role of the funding source

The sponsor of the study had no role in study design, data extraction, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had responsibility for the decision to submit for publication.
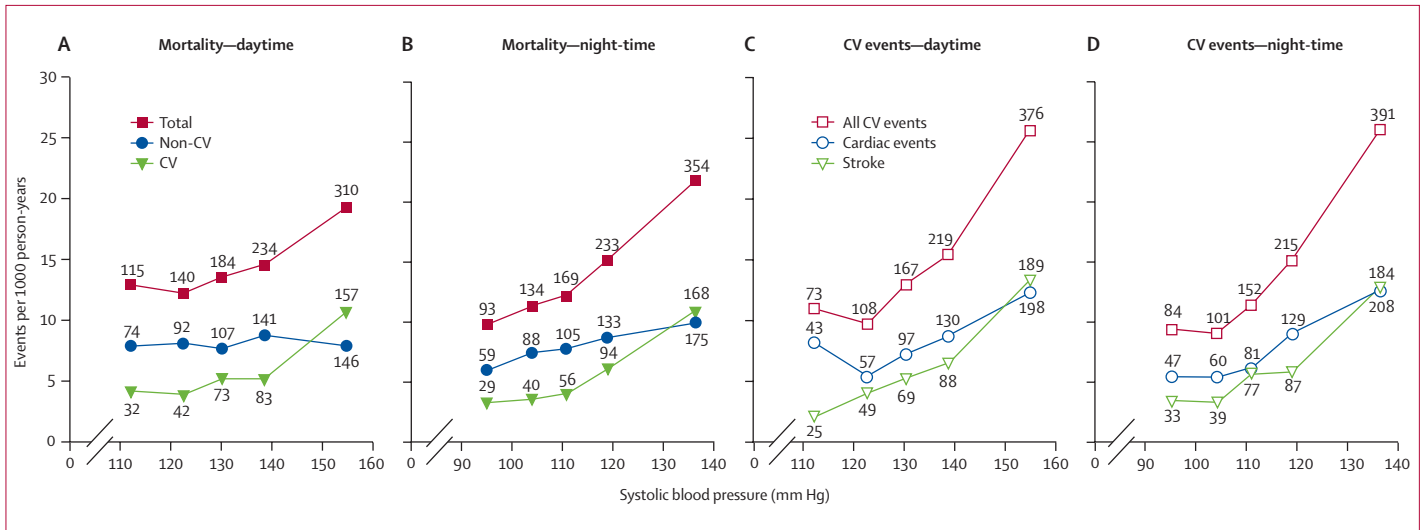
Figure 1: Incidence of mortality (A, B) and cardiovascular events (C, D) by quintiles of the distributions of the daytime and night-time blood pressures in 7458 participants
CV=cardiovascular. Incidence rates were standardised for cohort, sex, and age by the direct method. Mortality rates are plotted separately for total, non-cardiovascular, and cardiovascular deaths. Cardiovascular events include fatal and non-fatal endpoints and are given for all cardiovascular events combined, stroke, and cardiac events. The number of endpoints contributing to the rates is shown.

Results

The study population consisted of 4358 (58%) people from Europe, 1666 (22%) from Asia, and 1434 (19%) from South America. 3416 (46%) of the participants were women, and 3436 (46%) had hypertension on conventional blood pressure measurement, 1637 (48%) of whom were taking drugs to lower their blood pressure.

Mean age was 56·8 (SD 13·9) years. The mean conventional blood pressure was 132·4 (20·8) mm Hg systolic and 80·1 (11·6) mm Hg diastolic. For the 24-h blood pressure, these values were 124·8 (14·5) mm Hg and 74·0 (8·5) mm Hg, respectively. At enrolment, 2172 (29%) participants were current smokers and 3540 (48%) reported drinking alcohol. Table 1 shows the

	All	Stroke	Cardiac	Coronary
Number of events (%)	943 (13%)	420 (6%)	525 (7%)	390 (5%)
Daytime blood pressure				
Systolic				
Adjusted	1·33 (1·25–1·42)§	1·47 (1·34–1·62)§	1·25 (1·15–1·36)§	1·23 (1·11–1·36)§
Fully adjusted	1·16 (1·07–1·26)‡	1·27 (1·13–1·43)‡	1·11 (0·99–1·24)	1·19 (1·04–1·36)*
Diastolic				
Adjusted	1·25 (1·17–1·33)§	1·39 (1·26–1·53)§	1·15 (1·05–1·25)†	1·17 (1·06–1·30)†
Fully adjusted	1·11 (1·02–1·20)*	1·21 (1·07–1·37)†	1·04 (0·93–1·17)	1·11 (0·98–1·27)
Night-time blood pressure				
Systolic				
Adjusted	1·31 (1·24–1·38)§	1·40 (1·29–1·51)§	1·24 (1·16–1·34)§	1·16 (1·06–1·26)†
Fully adjusted	1·21 (1·12–1·30)§	1·23 (1·11–1·37)‡	1·17 (1·06–1·29)†	1·05 (0·93–1·18)
Diastolic				
Adjusted	1·28 (1·20–1·36)§	1·39 (1·26–1·52)§	1·18 (1·09–1·28)§	1·15 (1·05–1·27)†
Fully adjusted	1·20 (1·11–1·30)§	1·24 (1·10–1·39)‡	1·15 (1·04–1·28)†	1·08 (0·96–1·22)
Night-to-day blood pressure ratio				
Systolic				
Adjusted	1·11 (1·05–1·17)‡	1·09 (1·00–1·19)*	1·11 (1·02–1·19)*	1·01 (0·92–1·11)
Fully adjusted	1·05 (0·98–1·11)	1·02 (0·94–1·11)	1·05 (0·97–1·14)	0·97 (0·89–1·07)
Diastolic				
Adjusted	1·09 (1·02–1·16)†	1·07 (0·97–1·17)	1·09 (1·00–1·18)*	1·02 (0·93–1·13)
Fully adjusted	1·07 (1·00–1·13)*	1·04 (0·95–1·14)	1·07 (0·98–1·16)	1·00 (0·91–1·11)

Data are number (%) or standardised hazard ratios (95% CI). See table 2 legend for details of standardised hazard ratios. *p<0·05. †p<0·01. ‡p<0·001. §p<0·0001.

Table 3: Adjusted standardised hazard ratios for combined, fatal, and non-fatal cardiovascular endpoints
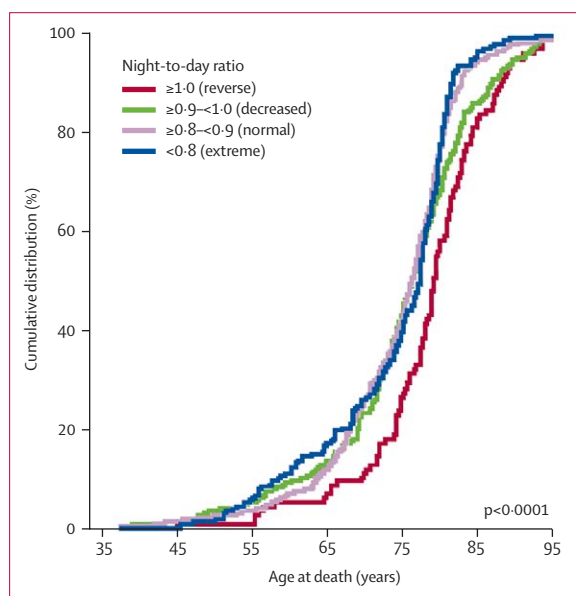
Figure 2: Cumulative incidence of age at death by category of the night-to-day ratio of systolic blood pressure
The p value refers to the difference between people classified as reverse and normal dippers.
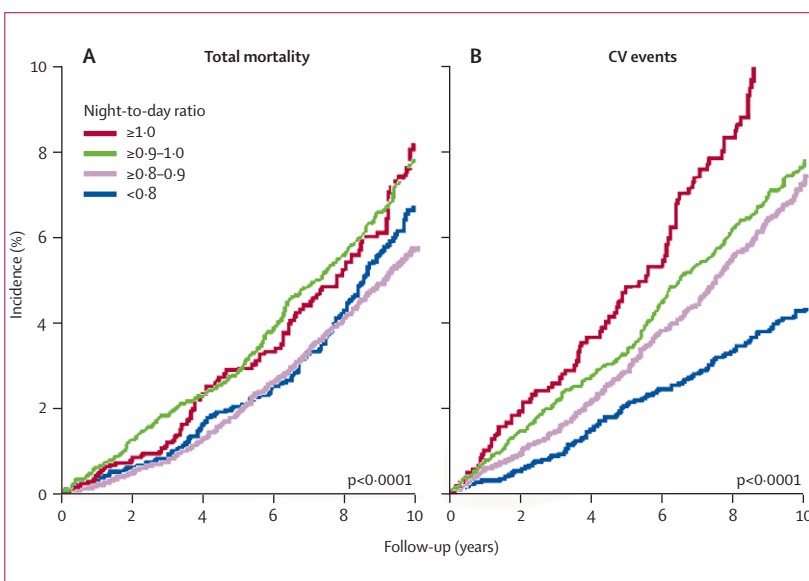

Figure 3: Kaplan-Meier survival function estimates for total mortality (A) and for all cardiovascular events (B) by category of the night-to-day ratio of systolic blood pressure
CV=cardiovascular. p values are for trend across the four categories. Incidence was adjusted for cohort, sex, age, body-mass index, smoking and drinking, serum total cholesterol, history of cardiovascular disease, diabetes mellitus, and antihypertensive drug treatment.

baseline characteristics by category of the systolic night-to-day ratio. Across the four groups, all characteristics differed significantly (table 1) with the exception of the proportion of women (p=0·16), body-mass index (p=0·08), and the conventional diastolic blood pressure (p=0·88). Table 1 also shows significance levels for the comparison of the night-to-day ratio categories with the subgroup with a normal night-to-day ratio (≥0·80 to <0·90). Participants with a night-to-day ratio of 1·00 or higher were older, were more likely to come from Asia and South America, and have a history of diabetes mellitus or previous cardiovascular complications, than those with a normal night-to-day ratio.

In the overall study population, the median follow-up was 9·6 years (5th to 95th percentile 2·5–13·7). Across cohorts, median follow-up ranged from 2·5 years (2·3–2·6) in JingNing to 13·1 years (1·1–15·7) in Noorderkempen. 983 participants died (14·1 per 1000 person-years) and 943 had a fatal or non-fatal cardiovascular complication (13·6 per 1000 person-years). There were more non-cardiovascular than cardiovascular deaths (table 2). Of the cause-specific first cardiovascular events, 51 were fatal strokes and 369 were non-fatal strokes. Cardiac events consisted of 146 fatal and 379 non-fatal events, including 65 fatal and 186 non-fatal cases of acute myocardial infarction, 30 deaths from ischaemic heart disease, 30 sudden deaths, 21 fatal and 142 non-fatal cases of heart failure, and 51 cases of surgical or percutaneous coronary revascularisation. Of the coronary revascularisation procedures, 18 took place in Noorderkempen, one in Copenhagen, and 32 in Montevideo.

	Extreme	Normal	Decreased	Reverse
Mortality				
Total				
Deaths (%)	182 (12%)	418 (11%)	265 (15%)	118 (27%)
Hazard ratio	0·93 (0·78–1·11)	referent	1·19 (1·02–1·39)*	1·56 (1·26–1·92)‡
Non-CV				
Deaths (%)	106 (7%)	238 (6%)	150 (9%)	66 (15%)
Hazard ratio	0·94 (0·75–1·19)	referent	1·25 (1·01–1·54)*	1·66 (1·25–2·20)†
CV				
Deaths (%)	73 (5%)	162 (4%)	102 (6%)	50 (11%)
Hazard ratio	0·97 (0·73–1·28)	referent	1·08 (0·84–1·39)	1·45 (1·02–2·02)*
Fatal and non-fatal CV events				
All				
Events (%)	178 (12%)	420 (11%)	237 (14%)	108 (25%)
Hazard ratio	0·87 (0·73–1·04)	referent	1·05 (0·88–1·23)	1·30 (1·04–1·62)*
Stroke				
Events (%)	81 (5%)	178 (5%)	113 (6%)	48 (11%)
Hazard ratio	0·95 (0·73–1·24)	referent	1·13 (0·89–1·44)	1·20 (0·87–1·67)
Cardiac				
Events (%)	99 (7%)	244 (7%)	125 (7%)	57 (13%)
Hazard ratio	0·84 (0·67–1·07)	referent	0·97 (0·78–1·22)	1·31 (0·97–1·77)
Coronary				
Events (%)	83 (6%)	185 (5%)	93 (5%)	29 (7%)
Hazard ratio	0·92 (0·71–1·20)	referent	0·99 (0·77–1·28)	0·92 (0·62–1·38)

CV=cardiovascular. Values for deaths and events are the number of participants, with the crude rate per 100 people given between parentheses. All hazard ratios express the risk versus normal (referent) and were adjusted for cohort, sex, age, body-mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, antihypertensive drug treatment, and the 24-h blood pressure. *p<0·05. †p<0·001. ‡p<0·0001.

Table 4: Adjusted hazard ratios (95% CI) associated with extreme, decreased, and reverse dipping versus normal dipping

	At risk	Events	Daytime	Night-time	Night-to-day ratio
Total mortality					
All participants	7458	983	0·94 (0·87–1·03)	1·22 (1·13–1·31)§	1·13 (1·07–1·19)§
Women	3416 (46%)	267 (27%)	0·97 (0·82–1·15)	1·35 (1·15–1·58)‡	1·16 (1·04–1·30)†
Men	4042 (54%)	716 (73%)	0·93 (0·84–1·02)	1·19 (1·09–1·29)§	1·12 (1·05–1·19)‡
<60 years	3756 (50%)	115 (12%)	1·12 (0·83–1·51)	1·20 (0·89–1·61)	1·06 (0·86–1·31)
≥60 years	3702 (50%)	868 (88%)	0·93 (0·85–1·02)	1·22 (1·13–1·31)§	1·13 (1·07–1·20)§
No history of CVD	6832 (92%)	787 (80%)	0·97 (0·88–1·06)	1·22 (1·12–1·32)§	1·12 (1·05–1·19)‡
History of CVD	626 (8%)	196 (20%)	0·89 (0·79–1·07)	1·23 (1·03–1·46)*	1·15 (1·02–1·31)*
Untreated	5821 (78%)	598 (61%)	0·98 (0·87–1·09)	1·20 (1·09–1·32)‡	1·11 (1·03–1·19)†
Treated	1637 (22%)	384 (39%)	0·89 (0·78–1·01)	1·24 (1·11–1·38)‡	1·16 (1·06–1·26)‡
Normotensive	4022 (54%)	315 (32%)	1·03 (0·86–1·24)	1·23 (1·04–1·44)*	1·09 (0·98–1·21)
Hypertensive	3436 (46%)	668 (68%)	0·91 (0·83–1·01)	1·22 (1·12–1·32)§	1·14 (1·07–1·22)§
All cardiovascular events					
All participants	7458	943	1·16 (1·07–1·26)‡	1·21 (1·12–1·30)§	1·05 (0·98–1·11)
Women	3416 (46%)	255 (27%)	1·21 (1·02–1·44)*	1·38 (1·18–1·63)§	1·09 (0·97–1·23)
Men	4042 (54%)	688 (73%)	1·12 (1·02–1·23)*	1·18 (1·09–1·28)§	1·05 (0·98–1·12)
<60 years	3756 (50%)	139 (15%)	1·55 (1·21–1·99)‡	1·22 (0·95–1·58)	0·94 (0·78–1·14)
≥60 years	3702 (50%)	804 (85%)	1·11 (1·02–1·21)*	1·21 (1·13–1·31)§	1·07 (1·00–1·13)*
No history of CVD	6832 (92%)	745 (79%)	1·19 (1·08–1·30)‡	1·22 (1·13–1·32)§	1·05 (0·98–1·11)
History of CVD	626 (8%)	198 (21%)	1·09 (0·91–1·30)	1·14 (0·97–1·34)	1·04 (0·92–1·17)
Untreated	5821 (78%)	531 (56%)	1·30 (1·15–1·45)§	1·15 (1·04–1·27)†	0·99 (0·91–1·07)
Treated	1637 (22%)	412 (44%)	1·01 (0·89–1·14)	1·27 (1·14–1·40)§	1·12 (1·03–1·21)†
Normotensive	4022 (54%)	252 (27%)	1·32 (1·09–1·60)†	1·26 (1·05–1·51)†	1·01 (0·90–1·14)
Hypertensive	3436 (46%)	691 (73%)	1·11 (1·01–1·22)*	1·20 (1·11–1·30)§	1·06 (0·99–1·13)

CVD=cardiovascular disease. Hypertension was a conventional blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic or the use of antihypertensive drugs. p values for heterogeneity are reported in the text. All hazard ratios were adjusted as described in table 2 legend. *p<0·05. †p<0·01. ‡p<0·001. §p<0·0001.

Table 5: Adjusted standardised hazard ratios (95% CI) for systolic blood pressure according to baseline characteristics

Figure 1 shows the rates of mortality and cardiovascular events standardised by cohort, sex, and age. Table 2 shows the multivariate-adjusted hazard ratios associated with every SD increase in the day and night blood pressures. The hazard ratios for the night-to-day ratios are shown in table 2 for mortality and in table 3 for fatal combined with non-fatal cardiovascular events.

In adjusted models, night-time blood pressure predicted all mortality outcomes, whereas daytime blood pressure predicted total and cardiovascular mortality, but not death from non-cardiovascular causes (table 2). In fully adjusted models, the night-time blood pressure was a significant predictor of total, cardiovascular, and non-cardiovascular mortality. In contrast, in the presence of night-time blood pressure, the daytime blood pressure was not significant for total and cardiovascular mortality, but was significant for non-cardiovascular mortality (table 2), with higher levels being associated with lower relative risk.

With adjustments applied for cohort and risk factors, the daytime and night-time systolic and diastolic blood pressures consistently predicted cardiovascular, cardiac, and coronary events, and fatal and non-fatal stroke

(table 3). In fully adjusted models, with correction for night-time blood pressure, the systolic daytime blood pressure lost its prognostic significance for cardiac events (hazard ratio 1·11; p=0·07), whereas the diastolic daytime blood pressure became non-significant for cardiac (1·04; p=0·45) and coronary (1·11; p=0·10) events (table 3). When adjusted for daytime blood pressure, the systolic and diastolic night-time levels no longer predicted coronary events (1·05; p=0·43 and 1·08; p=0·21, respectively).

In continuous analyses, the systolic and diastolic night-to-day ratios significantly predicted total, non-cardiovascular, and cardiovascular mortality in models adjusted for cohort and risk factors (table 2). This finding was also noted in fully adjusted models, which were additionally adjusted for 24-h blood pressure (table 2). The only exception was the fully adjusted association of cardiovascular mortality with the systolic night-to-day ratio (p=0·10). In contrast with mortality, the systolic and diastolic night-to-day ratios were not consistent predictors of fatal combined with non-fatal events (table 3). In fully adjusted models, the systolic night-to-day ratio was not significant (table 3) for all combined fatal and non-fatal outcomes investigated. The diastolic night-to-day ratio was only a significant predictor of all cardiovascular outcomes (p=0·04), but not of other combined fatal and non-fatal events (table 3).

Participants with higher night-time than daytime blood pressure were not only older at enrolment (table 1), but were also older when they died than were those with a normal night-to-day ratio (78·2 years *vs* 74·1 years; p<0·0001; figure 2). Both cardiovascular (78·9 years *vs* 75·9 years; p=0·002) and non-cardiovascular (77·5 years *vs* 73·6 years; p=0·001) mortality contributed to this finding.

Figure 3 shows Kaplan-Meier survival function estimates for total mortality and the composite cardiovascular endpoint by category of the systolic night-to-day ratio. With adjustments applied for cohort, cardiovascular risk factors, and the 24-h blood pressure, participants with higher night-time than daytime blood pressure or a less pronounced dip in blood pressure were associated with higher rates of total mortality and cardiovascular events than were those whose night-to-day blood pressure ratio was normal or extreme (p<0·0001). Table 4 provides the number of events per dipping class. Participants with higher night-time than daytime blood pressure had a significantly higher risk of death from any cause and more fatal and non-fatal cardiovascular complications than did those with a normal night-to-day ratio (table 4).

In sensitivity analyses involving total mortality and the composite of all fatal and non-fatal cardiovascular endpoints in relation to the daytime and night-time systolic blood pressure and the systolic night-to-day ratio, we stratified according to sex, median age (60 years), history of
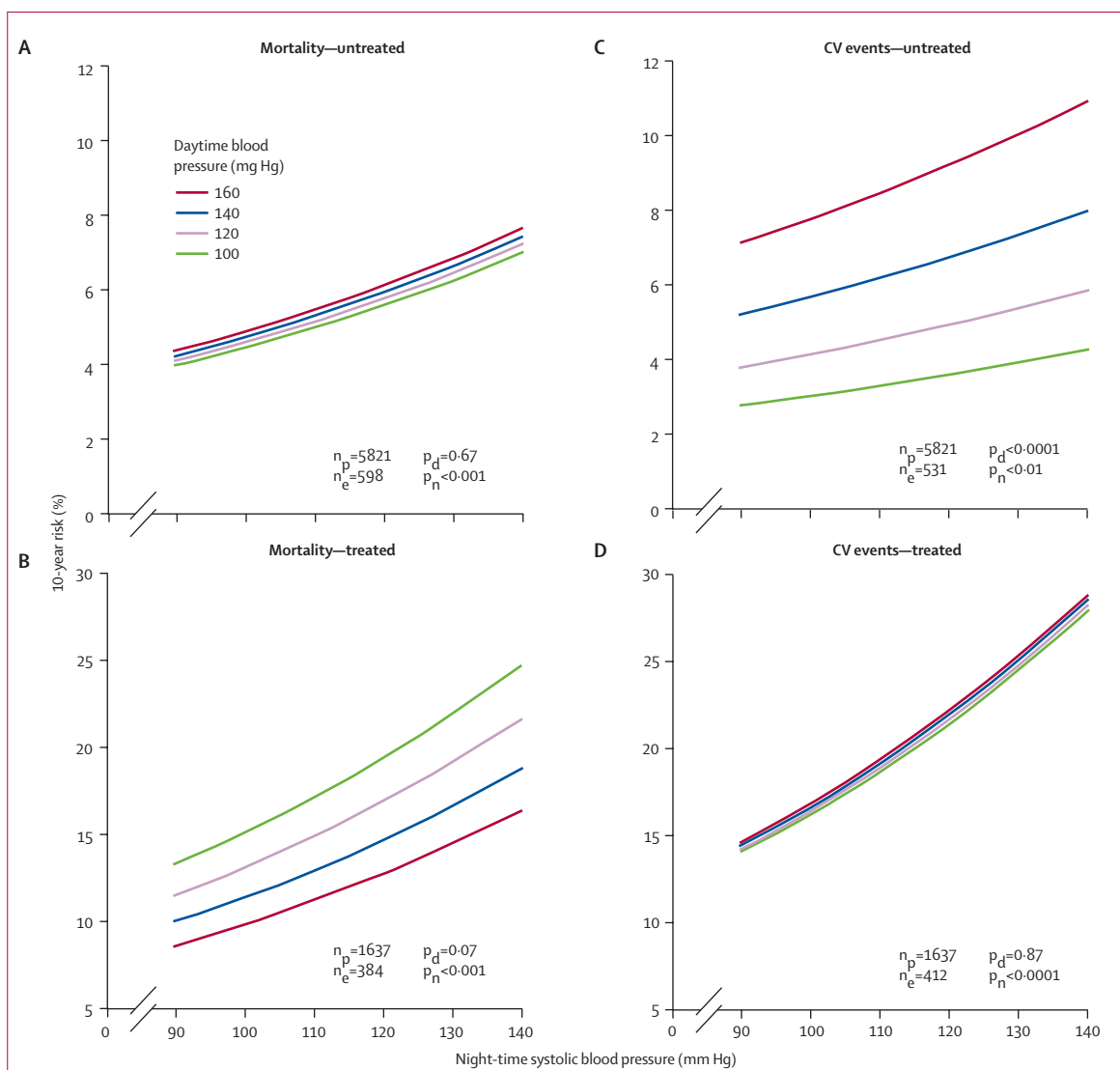
Figure 4: Absolute 10-year risk of death (A, B) or a cardiovascular event (C, D) in relation to systolic blood pressure by treatment status
The night-time blood pressure is plotted along the x axis and the scale covers the 5th to 95th percentile interval. The daytime blood pressure is represented by four risk functions corresponding to levels of 100, 120, 140, and 160 mm Hg. Risk estimates were adjusted as in figure 3. np and ne indicate the number of participants at risk and the number of events. pd and pn denote the significance of the independent contributions of the daytime and nighttime blood pressures. Addition of the interaction terms between the daytime and night-time blood pressures and treatment status greatly improved the fit of the models (log likelihood ratio test; p<0·0001).

cardiovascular disease, treatment status, and the presence or absence of hypertension on conventional blood pressure measurement (table 5). The results across these strata were consistent with those in the whole study population with few exceptions. Women had higher hazard ratios for cardiovascular events in relation to the daytime blood pressure than did men (1·21 vs 1·12; p=0·06), and higher hazard ratios for both total mortality (1·35 vs 1·19; p=0·02) and cardiovascular events (1·38 vs 1·18; p=0·006) in relation to the night-time blood pressure. In participants younger than 60 years and in those who were untreated, the hazard ratios for cardiovascular events in relation to the daytime blood pressure were significantly larger than were those in participants older than 60 years (1·55 vs 1·11;

p=0·02) and in treated patients (1·30 vs 1·01; p=0·005). Figure 4 shows the multivariate-adjusted and independent associations of total mortality and all cardiovascular events with the daytime and night-time blood pressures by treatment status at enrolment. Addition of the interaction terms between treatment status and the daytime and night-time blood pressures to the models greatly improved the fit (log likelihood ratio test p<0·0001).

Sensitivity analyses, in which we excluded one cohort at a time, produced consistent results for total mortality and the combined cardiovascular endpoint in relation to the daytime and night-time systolic and diastolic blood pressures, and the systolic night-to-day ratio treated as a continuous variable (table 6).

	At risk	Events	Daytime	Night-time	Night-to-day ratio
Total mortality					
All participants	7458	983	0·94 (0·87–1·03)	1·22 (1·13–1·31)§	1·13 (1·07–1·19)§
Copenhagen	5321 (71%)	735 (75%)	0·92 (0·84–1·02)	1·22 (1·12–1·32)§	1·13 (1·07–1·20)§
Ohasama	6141 (82%)	792 (81%)	0·97 (0·88–1·07)	1·19 (1·09–1·29)§	1·10 (1·03–1·17)†
Noorderkempen	6334 (85%)	847 (86%)	0·94 (0·86–1·02)	1·20 (1·12–1·30)§	1·12 (1·06–1·19)§
Uppsala	6361 (85%)	685 (70%)	0·91 (0·82–1·02)	1·32 (1·19–1·46)§	1·17 (1·09–1·26)§
Montevideo	6024 (81%)	887 (90%)	0·96 (0·87–1·04)	1·22 (1·13–1·31)§	1·12 (1·06–1·19)§
JingNing	7109 (95%)	969 (99%)	0·95 (0·87–1·03)	1·20 (1·11–1·30)§	1·12 (1·06–1·19)§
All cardiovascular events					
All participants	7458	943	1·16 (1·07–1·26)‡	1·21 (1·12–1·30)§	1·05 (0·99–1·11)
Copenhagen	5321 (71%)	691 (73%)	1·18 (1·08–1·30)‡	1·16 (1·07–1·25)‡	1·02 (0·96–1·08)
Ohasama	6141 (82%)	794 (84%)	1·15 (1·05–1·26)†	1·20 (1·11–1·29)§	1·04 (0·98–1·11)
Noorderkempen	6334 (85%)	844 (90%)	1·14 (1·05–1·25)†	1·21 (1·12–1·30)§	1·05 (1·00–1·12)
Uppsala	6361 (85%)	629 (67%)	1·13 (1·01–1·26)*	1·36 (1·22–1·51)§	1·11 (1·03–1·20)†
Montevideo	6024 (81%)	822 (87%)	1·16 (1·06–1·26)†	1·21 (1·12–1·30)§	1·05 (0·99–1·12)
JingNing	7109 (95%)	935 (99%)	1·16 (1·07–1·26)‡	1·20 (1·11–1·29)§	1·05 (0·99–1·11)

All hazard ratios were adjusted as described in table 2 legend. *p<0·05. †p<0·01. ‡p<0·001. §p<0·0001.

Table 6: **Adjusted standardised hazard ratios (95% CI) for systolic blood pressure excluding one cohort at a time**

Discussion

Our study has shown that the predictive accuracy of the daytime and night-time blood pressures and the night-to-day blood pressure ratio depended on the outcome under study. For fatal endpoints, the night-time blood pressure did better than the daytime blood pressure, and the night-to-day ratio predicted total, cardiovascular, and non-cardiovascular mortality. In contrast, for fatal combined with non-fatal outcomes, the daytime blood pressure did equally well as the night-time blood pressure, and the night-to-day ratio lost its prognostic accuracy in all participants and in those who were untreated. Our findings suggest that a less pronounced dip in blood pressure might just be a marker of pre-existing or concurrent disease, leading to a lower daytime blood pressure, or might be the result of the intake of drugs to lower blood pressure during daytime. The worse prognosis for participants with higher night-time than daytime blood pressure was not associated with shorter life expectancy.

We implemented a meta-analysis on the basis of data from individual participants. In terms of standardisation and quality, such an approach is better than undertaking a meta-analysis of aggregate data extracted from publications.[37] As well as mortality, we investigated non-fatal events, which accrued during the long-term follow-up. We hold databases on several cohorts of patients with hypertension.[7,10,38] We opted not to combine population samples and patient cohorts. In patients with hypertension, treatment to lower blood pressure might be a confounder with too large an effect to adjust for,[13] whereas in population studies, most hypertensive patients still remain untreated.[39] Many researchers

dichotomised dipping status with use of arbitrary thresholds. To compare our findings with those in other studies, our report included outcome results according to category of dipping.[8,31] However, in our main analyses, we treated the night-to-day blood pressure ratio as a continuous variable, adjusted for the 24-h blood pressure and other covariates.

Our findings challenge the commonly held view that night-time blood pressure has the greatest prognostic accuracy.[2,4,7,8,10–12] One possible explanation is that antihypertensive drug treatment is a major confounder, and our results accord with this notion. Patients with more severe hypertension and those with a history of cardiovascular complications are more likely to be treated[40] and to be at higher risk than are other patients. Furthermore, patients with hypertension take their drugs during daytime, and the activity that lowers blood pressure probably weans off at night. This mechanism predictably leads to a reduced daytime blood pressure, increased night-time blood pressure, and a decreased night-to-day blood pressure ratio. Addition to the Cox models of the interaction terms of the daytime and night-time blood pressures with treatment status substantially improved the fit (figure 4). Reduction of the daytime blood pressure might explain why in treated patients, the fully adjusted hazard ratio of the daytime blood pressure was less than unity (p=0·07) for total mortality and far from significant (p=0·87) for the composite of all fatal and non-fatal cardiovascular events.

Several hypothetical mechanisms support the plausibility of an enhanced cardiovascular risk associated with an increased night-to-day ratio or raised night-time blood pressure, such as changes in the sympathetic modulation of the night-time blood pressure,[41] disturbed baroreflex sensitivity,[42] sleep apnoea,[43] or an increased salt sensitivity necessitating a high blood pressure at night to drive pressure natriuresis.[44,45] Moreover, in terms of the measurement conditions, such as body position and physical activity, the night-time blood pressure is better standardised than is the daytime blood pressure. However, definitions of dipping categories depend on arbitrary thresholds. The use of systolic or diastolic blood pressure, or both, often produce inconsistent classification of the same person. The night-to-day blood pressure ratio is subject to regression-to-the-mean.[46] Dipping status has also a low reproducibility, with up to 40% of individuals from Europe[47] and Asia[48] changing status between repeat recordings. Correction for the diurnal variation in the hydrostatic gradient between the heart and the arm cuff did not improve the reproducibility of the night-to-day blood pressure ratio.[49] We showed that the classification according to dipping status is also vulnerable to antihypertensive drug treatment.

The consensus view in the published work is that higher night-time than daytime blood pressure has the worst prognosis. In keeping with present opinion, we noted that such people were at a higher risk of death

from all causes than were those with normal night-to-day ratio. However, the fully adjusted night-to-day ratio of systolic blood pressure was a weak predictor of fatal combined with non-fatal endpoints in continuous as well as categorical analyses. Both antihypertensive treatment and reverse causality might explain this discrepancy. Elderly patients (≥60 years) enrolled in the Systolic Hypertension in Europe trial[7] had their ambulatory blood pressure measured after a 3-month run-in period on placebo. In patients subsequently randomly assigned to a placebo, the night-time systolic blood pressure was a better predictor of cardiovascular mortality and morbidity than was the daytime level. A 10% increase in the systolic night-to-day blood pressure ratio was also associated with a 41% increased cardiovascular risk, which was independent of the 24-h ambulatory blood pressure. Randomisation to active treatment attenuated these associations to non-significance.

Furthermore, in keeping with present IDACO results (table 1), people with higher night-time than daytime blood pressure in other studies were not only more frequently on antihypertensive drug treatment,[8,11] but they were also older,[8,11,50] and more likely to have a history of diabetes mellitus[50] or previous cardiovascular disease[8,50] than were those whose night-to-day blood pressure ratio was normal. The night-to-day blood pressure ratio increases as age increases.[31] In our analyses, people with higher night-time than daytime blood pressure died at an older age than did those with a night-time dip in blood pressure. Thus, higher night-time than daytime blood pressure might be a marker rather than a cause of a poor outcome. The fully-adjusted inverse associations between non-cardiovascular mortality and the daytime blood pressure in all people (table 2) and between total mortality and the daytime blood pressure in those who were untreated (figure 4) also lend support to the interpretation of reverse causality.

Our study should be interpreted within the context of its potential limitations. First, the IDACO database consists of six population-based cohorts from three continents,[2–4,16,17,19] but our results might not yet be generally applicable. Therefore, we are presently collecting outcome results in additional cohorts.[15,18,19,21] Second, the six populations differed in anthropometric characteristics and lifestyle. Our analyses were multivariate-adjusted at the level of individual people, but we cannot exclude residual confounding. Sensitivity analyses showed that no one cohort had a disproportionately large effect. Third, in long-term international surveys, the definition of clinical events, such as coronary heart disease, is probably less precise than it is in short-term studies or randomised clinical trials, in which endpoints are obtained via a single channel of information. However, we used only hard outcomes, excluding transient ischaemic attacks and angina pectoris. Fourth, experts usually regard the asleep and awake blood pressures to be the best standards to analyse the diurnal blood pressure profile.[51,52] However,

we previously noticed in people from Europe[29] and China[17] that short fixed clock-time intervals, which eliminate the transition periods in the morning and evening when blood pressure rapidly changes, result in daytime and night-time blood pressure means that are within 1–2 mm Hg of the awake and asleep levels.[17,29] Fifth, ambulatory blood pressure monitoring was not standardised across the six contributing studies in terms of device type and intervals between readings. However, we used the same programme to compute blood pressure means that were time weighted across cohorts. Finally, we could not adjust for antihypertensive drug treatment as a time-dependent covariate, because this information was only available for individuals in the Belgian cohort.[16,34] However, the proportion of our patients on antihypertensive treatment at baseline was only 22%. During the course of follow-up, the proportion of treated patients, in view of the poor rates of treatment in the general population[39] and the bad persistence of treatment in some clinical studies,[40] should have been greatly lower than in cohorts of referred patients with hypertension, who were followed up at specialised hypertension centres[6,38] or started on antihypertensive treatment at enrolment.[9]

Our findings have implications for clinical practice and research. The night-time blood pressure predicted mortality and non-fatal outcomes, irrespective of treatment status. The daytime blood pressure independently predicted the composite of all fatal and non-fatal cardiovascular events, especially in untreated participants. Our findings therefore support recording the ambulatory blood pressure during the whole day. The proposed thresholds for the 24-h blood pressure,[14] rather than the dipping pattern, should inform clinical decisions. Chronotherapy[53] means timing the administration of antihypertensive drugs in such a way that the blood pressure is lowered over 24 h, while a normal night-to-day blood pressure ratio is preserved. However, there is no evidence supporting the efficacy of chronotherapy in terms of blood pressure control[54] or outcome.[47] Furthermore, the classification of patients according to the night-to-day blood pressure ratio greatly depends on arbitrary criteria, is poorly reproducible,[47,48] and has a different prognostic meaning according to the disease outcome under study, the prevailing 24-h blood pressure level, and treatment status. We would therefore recommend that in future publications any categorical representation of the night-to-day ratio be supported by continuous analyses adjusted for the 24-h blood pressure and be stratified for treatment status.

References
1   O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. *Lancet* 1988; **332:** 397.
2   Ohkubo T, Hozawa A, Yamaguchi J, et al. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. *J Hypertens* 2002; **20:** 2183–89.
3   Hansen TW, Jeppesen J, Rasmussen F, Ibsen H, Torp-Pedersen C. Ambulatory blood pressure monitoring and mortality: a population-based study. *Hypertension* 2005; **45:** 499–504.
4   Ingelsson E, Björklund K, Lind L, Ärnlöv J, Sundström J. Diurnal blood pressure pattern and risk of congestive heart failure. *JAMA* 2006; **295:** 2859–66.
5   Mancia G, Facchetti R, Bombelli M, Grassi G, Sega R. Long-term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure. *Hypertension* 2006; **47:** 846–53.
6   Verdecchia P, Porcellati C, Schillaci G, et al. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension* 1994; **24:** 793–801.
7   Staessen JA, Thijs L, Fagard R, et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *JAMA* 1999; **282:** 539–46.
8   Kario K, Pickering TG, Matsuo T, Hoshide S, Schwartz JE, Shimada K. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension* 2001; **38:** 852–57.
9   Clement DL, De Buyzere ML, De Bacquer DA, et al. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med* 2003; **348:** 2407–15.
10   Dolan E, Stanton A, Thijs L, et al. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality. The Dublin Outcome Study. *Hypertension* 2005; **46:** 156–61.
11   Ben-Dov IZ, Kark JD, Ben-Ishay D, Mekler J, Ben-Arie L, Bursztyn M. Predictors of all-cause mortality in clinical ambulatory monitoring. Unique aspects of blood pressue during sleep. *Hypertension* 2007; **49:** 1235–41.
12   Schwartz GL, Bailey KR, Mosley T, et al. Association of ambulatory blood pressure with ischemic brain injury. *Hypertension* 2007; **49:** 1228–34.
13   Thijs L, Hansen TW, Kikuya M, et al. The International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome (IDACO): protocol and reseacrh perspectives. *Blood Press Monit* 2007; **12:** 255–62.
14   Kikuya M, Hansen TW, Thijs L, et al. Diagnostic thresholds for ambulatory blood pressure monitoring based on 10-year cardiovascular risk. *Circulation* 2006; **115:** 2145–52.
15   Kuznetsova T, Malyutina S, Pello E, Thijs L, Nikitin Y, Staessen JA. Ambulatory blood pressure of adults in Novosibirsk, Russia: interim report on a population study. *Blood Press Monit* 2000; **5:** 291–96.
16   Staessen JA, Bieniaszewski L, O'Brien ET, Imai Y, Fagard R. An epidemiological approach to ambulatory blood pressure monitoring: the Belgian population study. *Blood Press Monit* 1996; **1:** 13–26.
17   Li Y, Wang JG, Gao HF, et al. Are published characteristics of the ambulatory blood pressure generalizable to rural Chinese? The JingNing population study. *Blood Press Monit* 2005; **10:** 125–34.
18   O'Brien E, Murphy J, Tyndall A, et al. Twenty-four-hour ambulatory blood pressure in men and women aged 17 to 80 years: the Allied Irish Bank Study. *J Hypertens* 1991; **9:** 355–60.
19   Schettini C, Bianchi M, Nieto F, Sandoya E, Senra H, Hypertension Working Group. Ambulatory blood pressure. Normality and comparison with other measurements. *Hypertension* 1999; **34** (part 2): 818–25.
20   Shiburi CP, Staessen JA, Maseko M, et al. Reference values for SphygmoCor measurements in South Africans of African ancestry. *Am J Hypertens* 2006; **19:** 40–46.
21   Casiglia E, Basso G, Guglielmi F, et al. German origin clusters for high cardiovascular risk in an Italian enclave. *Int Heart J* 2005; **46:** 489–500.
22   Imai Y, Nagai K, Sakuma M, et al. Ambulatory blood pressure of adults in Ohasama, Japan. *Hypertension* 1993; **22:** 900–12.
23   O'Brien E, Mee F, Atkins N, Thomas M. Evaluation of three devices for self-measurement of blood pressure according to the revised British Hypertension Society Protocol: the Omron HEM-705 CP, Philips HP5332 and Nissei DS-175. *Blood Press Monit* 1996; **1:** 55–62.
24   Taylor R, Chidley K, Goodwin J, Broeders M, Kirby B. Accutracker II (version 30/23) ambulatory blood pressure monitor: clinical validation using the British Hypertensin Society and Association for the Advancement of Medical Instrumentation standards. *J Hypertens* 1993; **11:** 1275–82.
25   Groppelli A, Omboni S, Parati G, Mancia G. Evaluation of noninvasive blood pressure monitoring devices Spacelabs 90202 and 90207 versus resting and ambulatory 24-hour intra-arterial blood pressure. *Hypertension* 1992; **20:** 227–32.
26   Imai Y, Sasaki S, Minami N, et al. The accuracy and performance of the A&D TM 2421, a new ambulatory blood pressure monitoring device based on the cuff-oscillometric method and the Korotkoff sound technique. *Am J Hypertens* 1992; **5:** 719–26.

27 Imai Y, Abe K, Sasaki S, et al. Determination of clinical accuracy and nocturnal blood pressure pattern by new portable device for monitoring indirect ambulatory blood pressure. *Am J Hypertens* 1990; **3:** 293–301.

28 Ohkubo T, Imai Y, Tsuji I, et al. Reference values for 24-hour ambulatory blood pressure monitoring based on a prognositic criterion. The Ohasama Study. *Hypertension* 1998; **32:** 255–59.

29 Fagard R, Brguljan J, Thijs L, Staessen J. Prediction of the actual awake and asleep blood pressures by various methods of 24 h pressure analysis. *J Hypertens* 1996; **14:** 557–63.

30 Franklin SS, Larson MG, Khan SA, et al. Does the relation of blood pressure to coronary heart disease change with aging? The Framingham Heart Study. *Circulation* 2001; **103:** 1245–49.

31 Staessen JA, Bieniaszewski L, O'Brien E, et al. Nocturnal blood pressure fall on ambulatory monitoring in a large international database. *Hypertension* 1997; **29:** 30–39.

32 Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003; **26** (suppl 1)**:** S5–S20.

33 Ohkubo T, Kikuya K, Metoki H, et al. Prognosis of "masked" hypertension and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring. 10-year follow-up from the Ohasama study. *J Am Coll Cardiol* 2005; **46:** 508–15.

34 Li Y, Thijs L, Kuznetsova T, et al. Cardiovascular risk in relation to α-adducin *Gly460Trp* polymorphism and systolic pressure. A prospective population study. *Hypertension* 2005; **46:** 527–32.

35 Hansen TW, Jeppesen J, Rasmussen S, Ibsen H, Torp-Pedersen C. Ambulatory blood pressure and risk of cardiovascular disease: a population based study. *Am J Hypertens* 2006; **19:** 243–59.

36 Pocock S, Clayton TC, Altman DG. Survival plot of time-to-event outcomes in clinical trials. *Lancet* 2002; **359:** 1686–89.

37 Stewart LA, Parmar MKB. Meta-analysis of the literature or of individual patient data: is there a difference? *Lancet* 1993; **341:** 418–22.

38 Celis H, Staessen JA, Thijs L, et al. Cardiovascular risk in white-coat and sustained hypertensive patients. *Blood Press* 2002; **11:** 352–56.

39 Weinehall L, Öhgren B, Persson M, et al. High remaining risk in poorly treated hypertension: the 'rule of halves' still exist. *J Hypertens* 2002; **20:** 2081–88.

40 Chapman RH, Benner JS, Petrilla AA, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med* 2005; **165:** 1147–52.

41 Dodt C, Breckling U, Derad I, Fehm HL, Born J. Plasma epinephrine and norepinephrine concentrations of healthy humans associated with nighttime sleep and morning arousal. *Hypertension* 1997; **30** (part 1)**:** 71–76.

42 Vaile JC, Stallard TJ, al-Ani M, Jordan PJ, Townend JN, Littler WA. Sleep and blood pressure: spontaneous baroreflex sensitivity in dippers and non-dippers. *J Hypertens* 1996; **14:** 1427–32.

43 Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea. A population health perspective. *Am J Respir Crit Care Med* 2002; **165:** 1217–39.

44 Staessen JA, Birkenhäger W, Bulpitt CJ, et al. The relationship between blood pressure and sodium and potassium excretion during the day and at night. *J Hypertens* 1993; **11:** 443–47.

45 Sachdeva A, Weder AB. Nocturnal sodium excretion, blood pressure dipping, and sodium sensitivity. *Hypertension* 2006; **48:** 527–33.

46 Staessen J, Bulpitt CJ, O'Brien E, et al. The diurnal blood pressure profile. A population study. *Am J Hypertens* 1992; **5:** 386–92.

47 Omboni S, Parati G, Palatini P, et al. Reproducibility and clinical value of nocturnal hypotension: prospective evidence from the SAMPLE study. *J Hypertens* 1998; **16:** 733–38.

48 Mochizuki Y, Okutani M, Donfeng Y, et al. Limited reproducibility of circadian variation in blood pressure dippers and nondippers. *Am J Hypertens* 1998; **11:** 403–09.

49 Parati G. Blood pressure reduction at night: sleep and beyond. *J Hypertens* 2000; **18:** 1725–29.

50 Davidson MB, Hix JK, Vidt DG, Brotman DJ. Association of impaired diurnal blood pressure variation with a subsequent decline in glomerular filtration rate. *Arch Intern Med* 2006; **166:** 846–52.

51 O'Brien E, Asmar R, Beilin L, et al. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. *J Hypertens* 2005; **23:** 697–701.

52 Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals. Part 1: blood pressure measurement in humans. A statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* 2005; **45:** 142–61.

53 Scarpelli PT, Gallo M, Chiari G. Chronobiology of blood pressure. *J Nephrol* 2000; **13:** 197–204.

54 Hermida RC, Calvo C, Ayala DE, et al. Administration time-dependent effects of valsartan on ambulatory blood pressure in hypertensive subjects. *Hypertension* 2003; **42:** 283–90.