Masked hypertension in Diabetes Mellitus: Treatment Implications for Clinical Practice

Short title: Masked hypertension in diabetes mellitus

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Expanded Methods

Study Population

As described in detail elsewhere,[1] 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 the ambulatory blood pressure and cardiovascular risk factors was available, and if the subsequent follow-up included both fatal and nonfatal outcomes. All participants gave informed written consent. Subjects recruited in Kraków, Novosibirsk, Pilsen, and Padova took part in the European Project on Genes in Hypertension (EPOGH).[2]

Blood Pressure Measurements

Conventional blood pressure was measured by trained observers with a mercury sphygmomanometer,[2-8] with validated auscultatory[9] (USM-700F, UEDA Electronic Works, Tokyo, Japan) or oscillometric[10] (OMRON HEM-705CP, Omron Corporation, Tokyo, Japan) devices, using the appropriate cuff size, with participants in the sitting[2,3,5-10] or supine[4] position. Conventional blood pressure was the average of 2 consecutive readings obtained either at the person's home[2,5,6,8,10] or at an examination center.[3,4,7,9] We programmed portable monitors to obtain ambulatory blood pressure readings at 30 minute intervals throughout the whole day,[7,9] or at intervals ranging from 15[3] to 30[4] minutes during daytime and from 30[3] to 60[4] minutes at night. The devices implemented an auscultatory algorithm (Accutracker II) in Uppsala[4] or an oscillometric technique (SpaceLabs 90202 and 90207, Nippon Colin, and ABPM 630) in the other cohorts.[2,3,5-10]

The same SAS progam processed all ambulatory recordings, which generally stayed unedited. The Ohasama recordings were edited sparsely according to previously published criteria.[11] Within individual subjects, we weighted the means of the ambulatory blood pressure by the interval between readings. 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[2-5,7,8] and South America,[10] and from 0800 h to 1800 h in those from Asia.[6,9] The corresponding night-time intervals ranged from midnight to 0600 h[2-5,7,8,10] and from 2200 h to 0400 h.[6,9] 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.[6,12]

We categorized the conventional blood pressure according to the JNC7 [13] guidelines. Normotension was a level lower than 140 mm Hg systolic and 90 mm Hg diastolic. Stage 1 hypertension encompassed 140 to 159 mm Hg systolic or 90 to 99 mm Hg diastolic. Conventional blood pressures of at least 160 mm Hg systolic or 100 mm Hg diastolic were classified as stage 2 hypertension. Ambulatory hypertension was a daytime blood pressure of 135 mm Hg systolic or 85 mm Hg diastolic or more.[14] Sustained normotension was normotension on both conventional and ambulatory measurement. Masked hypertension was ambulatory hypertension in participants with a normal conventional blood pressure. Patients on antihypertensive drug treatment were classified according to their treated blood pressure. The term 'normotension' in treated subjects refer to successfully treated hypertensive patients, i.e. hypertensive subjects whose blood pressure, both CBP and ABP, are controlled on antihypertensive drug therapy.

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. Body mass index 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,[2,4-6,8-10,15], a fasting blood glucose concentration of at least 7.0 mmol/L,[2,4-6,8-10,15] a random blood glucose concentration of at least 11.1 mmol/L,[2,5,6,8,9] a self-reported diagnosis,[2,5-8,10] or diabetes documented in practice or hospital records.[10] To measure the serum creatinine concentration, all laboratories applied Jaffe's method[16] with the modifications described elsewhere[17,18] to overcome interferences and limitations. The samples were run on automated analyzers in certified laboratories that participated in external quality control programs. We used the Modification of Diet in Renal Disease (MDRD) Study equation[19] to estimate the glomerular filtration rate (GFR) from sex, age, and the serum creatinine concentration.

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.[20-22] The composite cardiovascular endpoint included fatal and non-fatal stroke, transient ischemic attacks, death from ischemic heart disease, sudden death, nonfatal myocardial infarction, angina pectoris, coronary revascularization, fatal and non-fatal heart failure and fatal and non-fatal peripheral arterial disease. A restricted definition of the composite cardiovascular endpoint not including transient ischemic attacks, angina pectoris and non-fatal peripheral arterial disease, was used for sensitivity analyses. In the Danish[15] and Swedisch cohorts,[4] the diagnosis of heart failure required hospitalization. In the Uruguayan cohort[10] the diagnosis of heart failure required dyspnea and a left ventricular ejection fraction of less than 40%. In the other cohorts,[2,5-9] heart failure was either a clinical diagnosis or the diagnosis on the death certificate, but in all cases, validated against hospital records or the records held by general practitioners. In all outcome analyses, we only considered the first event within each category.

Statistical Analysis

For database management and statistical analysis, we used SAS software, version 9.3 (SAS Institute, Cary, NC). For comparison of means and proportions, we applied the large-sample z-test and the χ^2-statistic, respectively. The risk association with masked hypertension was assessed using Cox regression analysis, stratified for cohort and adjusted for for sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus. To stratify for cohort, we pooled participants recruited in the framework of the European Project on Genes in Hypertension (Kraków, Novosibirsk, Padova, and Pilsen). We ascertained that the proportional hazard assumption underlying the Cox regression models was fulfilled by testing the interaction between the BP categories and follow-up time. We compared hazard ratios between groups by testing the significance of the appropriated interaction term. Statistical significance was an α-level of less than 0.05 on two-sided tests.

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Table S1. Baseline Characteristics of the 3259 Conventional Hypertensive Subjects Broken Down by Treatment Status, Diabetic Status and Ambulatory Blood Pressure Category

	Untreated				Treated			
	Non-diabetics		Diabetics		Non-diabetics		Diabetics	
Characteristic	Stage 1 HT (n=1443)	Stage 2 HT (n=528)	Stage 1 HT (n=93)	Stage 2 HT (n=47)	Stage 1 HT (n=564)	Stage 2 HT (n=417)	Stage 1 HT (n=96)	Stage 2 HT (n=71)
Number with characteristic (%)								
Male	937 (64.9)	367 (69.5)	63 (67.7)	42 (89.4)†	293 (52.0)	264 (63.3)§	62 (64.6)	54 (76.1)§
History of CV events	85 (5.9)	51 (9.7)†	6 (6.5)	3 (6.4)	105 (18.6)	84 (20.1)	24 (25.0)	21 (29.6)
Current smokers	394 (27.5)	116 (22.0)	19 (20.4)	16 (34.8)	105 (18.7)	78 (18.8)	15 (16.1)	14 (19.7)
Current drinkers	816 (61.9)	309 (65.2)	46 (58.2)	26 (70.3)	269 (54.5)	207 (56.9)	36 (50.7)	31 (57.4)
BMI>25kg/m²	896 (62.1)	332 (62.9)	71 (76.3)	36 (76.6)	356 (63.1)	285 68.3)	69 (71.9)	55 (77.5)
BMI>30kg/m²	241 (16.7)	108 (20.5)	28 (30.1)	16 (34.0)	117 (20.7)	95 (22.8)	35 (36.5)	20 (28.2)
Mean values±SD								
Age, years	57.7±13.6	61.3±11.6§	62.4±11.4	64.8±8.1	64.5±10.0	65.2±10.2	66.3±9.1	66.9±7.6
Body mass index, kg/m^2	26.4±4.1	26.7±4.2	28.0±5.1	28.3±4.6	26.7±4.4	27.2±4.7	28.5±5.6	28.0±4.2
Blood glucose, mmol/L	93.3±14.5	96.4±16.2‡	155.4±49.8	148.2±54.6	99.1±17.5	98.2±17.5	153.2±57.6	153.4±40.7
Serum cholesterol, mmol/L	5.9±1.2	5.9±1.1	5.7±1.1	5.9±1.3	5.9±1.2	5.9±1.1	5.6±1.2	5.9±1.1
Serum creatinine, µmol/L	91.8±17.5	94.0±21.5	87.6±18.9	87.5±16.6	92.4±17.1	95.5±21.6	95.2±18.0	94.8±23.8
GFR, mL/min/1.73m²	75.1±15.0	73.2±15.9	78.6±15.4	83.3±19.2	70.5±14.0	69.8±14.6	69.5±12.9	72.7±15.3
Conventional SBP, mmHg	143.9±8.3	165.7±14.9§	146.5±7.7	170.3±15.6§	146.5±7.8	170.3±13.8§	147.7±6.3	169.8±14.2§
Conventional DBP, mmHg	87.2±7.6	96.9±10.8§	85.8±8.7	95.4±11.9§	86.2±8.6	95.8±11.4§	83.7±10.0	93.5±10.5§
Daytime SBP, mmHg	137.7±12.3	149.2±15.6§	141.9±15.0	146.5±15.1	138.3±13.0	146.7±15.5§	140.1±14.9	147.8±14.7†
Daytime DBP, mmHg	83.0±8.3	89.0±11.2§	83.2±9.7	85.1±10.2	81.8±8.8	86.2±10.7§	80.8±8.9	85.3±9.5†
Nighttime SBP, mmHg	117.7±13.7	129.4±17.1§	121.7±15.9	125.5±15.9	120.4±14.9	128.9±18.0§	125.6±17.6	128.8±17.1
Nighttime DBP, mmHg	67.8±8.4	73.9±11.3§	68.4±9.1	70.5±9.9	68.1±9.4	72.3±11.4§	69.6±10.0	70.7±9.6

HT, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; GFR, glomerular filtration rate, SD, standard deviation.
Stage 1 HT encompassed conventional blood pressures of 140-159/90-99 mmHg. Stage 2 HT is a conventional blood pressure ≥ 160/100 mmHg. GFR was estimated using the Modification of Diet in Renal Disease (MDRD) Study equation.[19] To convert blood glucose, serum cholesterol and serum creatinine from SI units to mg/dL, divide by 0.0555, 0.0259 and 88.4, respectively. Significance of the difference between stage 1 HT and stage 2 HT: *P<0.05; †P<0.01; ‡P<0.001;§P<0.0001

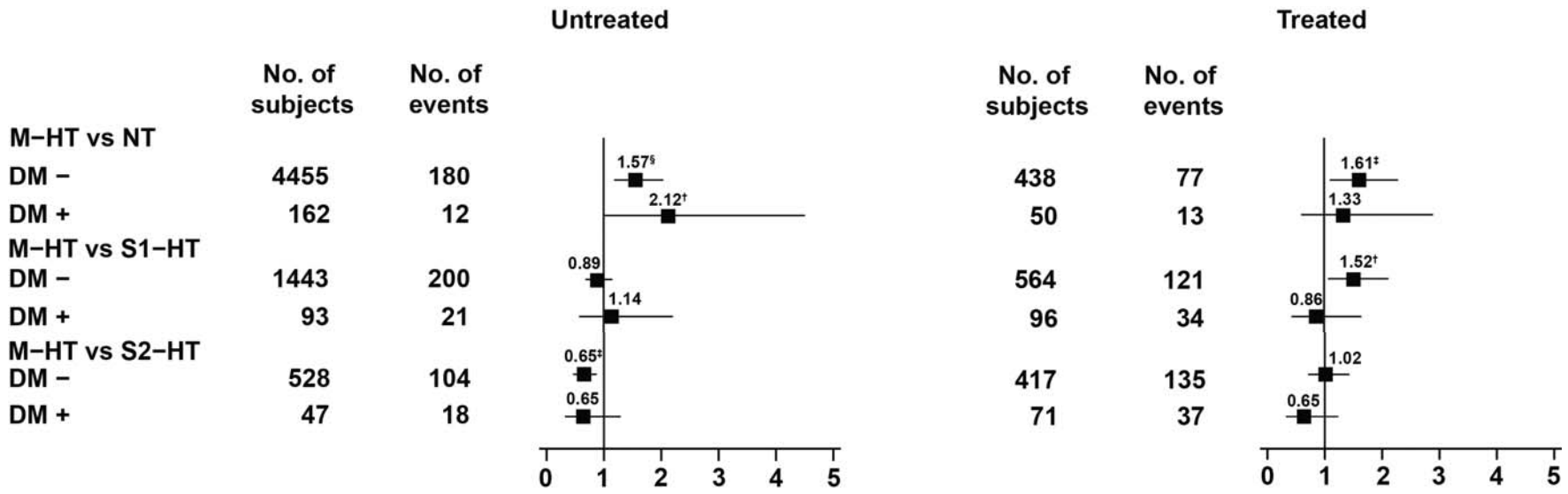

Figure S1. Hazard ratios for the **restricted** composite cardiovascular endpoint in untreated (left panel) and treated (right panel) conventional normotensive subjects without (DM-) and with (DM+) diabetes and with masked hypertension (M-HT, conventional blood pressure (CBP) < 140/90 mmHg and daytime ambulatory blood pressure (dABP) ≥ 135/85 mmHg). The sustained normotensives (NT, CBP < 140/90 mmHg and dABP < 135/85 mmHg), stage-1 hypertensives (S1-HT, CBP 140-159/90-94 mmHg) and stage-2 hypertensives (S2-HT, CBP ≥ 160/95 mmHg) were used as reference groups. Horizontal lines denote the 95% confidence interval. All analyses were adjusted for cohort, sex, age, body mass index, smoking and drinking, history of cardiovascular disease and total serum cholesterol. Numbers are the number of subjects (left column) and number of events (right column) in the reference groups. Significance of the hazard ratios: *0.05≤*P*<0.06; †*P*<0.05; ‡*P*<0.01;§P<0.001

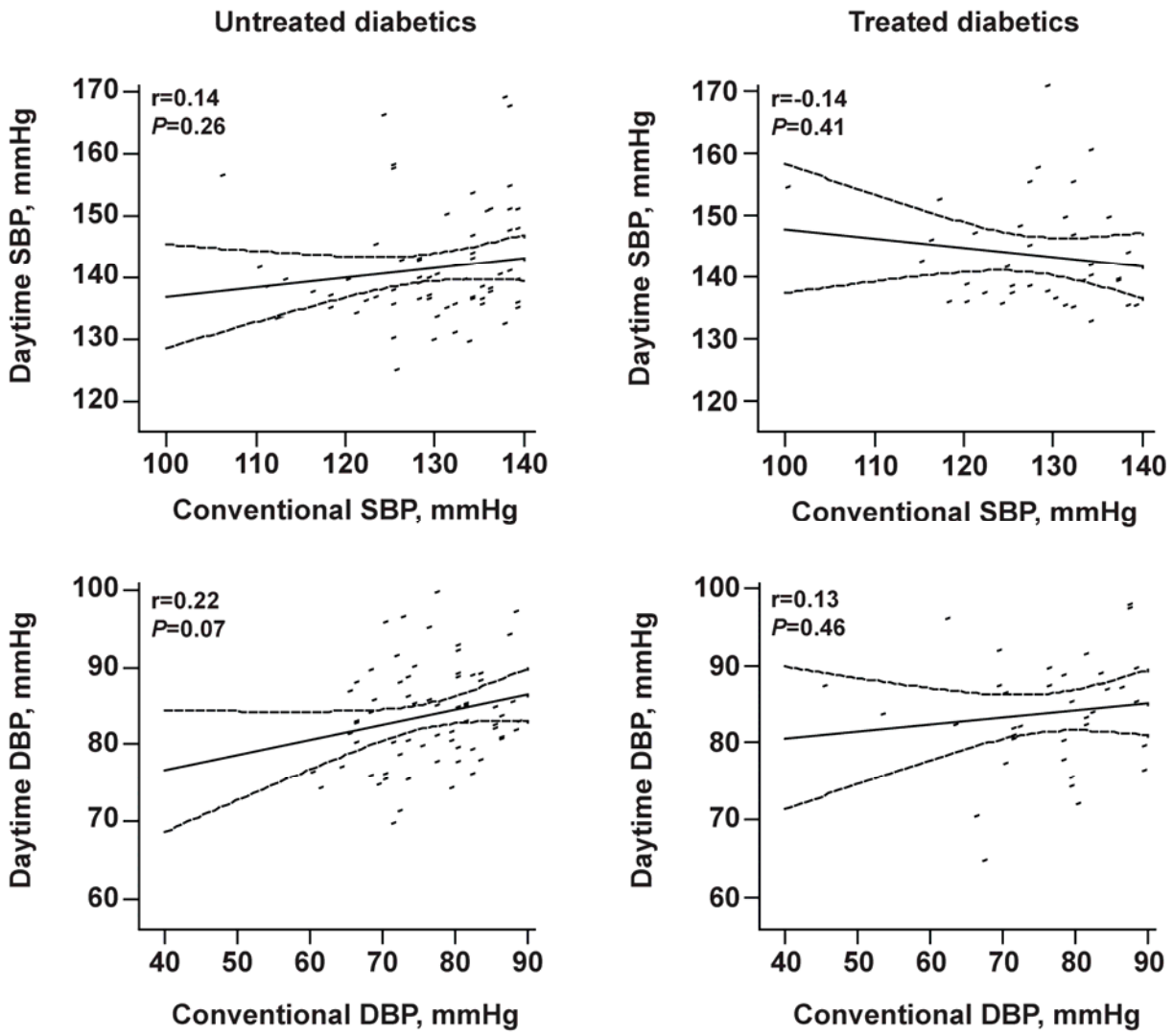

Figure S2. Association between the daytime and conventional blood pressures in 67 untreated (left panels) and 37 treated (right panels) diabetic subjects with masked hypertension. The upper panels show the systolic blood pressures (SBP); the lower panels the diastolic blood pressures (DBP). The regression lines, 95% confidence bands of the mean, Pearson correlation coefficients (r) and corresponding P-values are provided.