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The importance of beta-blocker treatment in diabetic hypertensive patients with different dipper patterns, in particular on the nocturnal non-dipper profile

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Abstract

Ambulatory blood pressure monitoring (ABPM) is the access way to the dippers' status in diabetic hypertensive patients, and it reveals the effects of antihypertensive medication in different dipper patterns. Of patients with consecutive type 2 diabetes mellitus (DM) patients with high blood pressure (HBP), 166 were treated with angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta-blockers (βB), calcium channel blockers (CCB), diuretics and different combinations of them, and were subjected to 24 hours' ABPM. We assessed the BP (blood pressure) circadian variation, variability of resting mean heart rate (MHR), and the correlations with the variety of drug combinations. There were 80 non-dippers (48.20%), 22 reverse dippers (13.26%), 57 dippers (34.34%) and 7 extreme-dippers (4.20%). Non-dippers treated with βB (67.50%) had lower 24 h/MHR – 72.46 bpm *vs.* 78.00 bpm (p=0.015) of those without βB, night MHR – 68.77 bpm *vs.* 73.26 bpm (p=0.038) and day MHR – 74.61 bpm *vs.* 81.50 bpm (p=0.005). Dippers had lowered MAP – 89.77 mmHg and MHR – 71.61 beats per minute (bpm) compared with 91.80 mmHg and 74.26 bpm found in non-dippers (p=0.29; p=0.13). Dippers were treated with ACEI (63.16%), ARB (19.30%), CCB (40.35%), combinations of these (12.28%), βB (59.65%), diuretics (75.44%). The non-dippers diabetics have increased MHR and MAP as compared to dippers, but non-dippers treated with beta-blockers have significantly lower MHR and MAP than those without BB. Treatment of BP with beta-blockers does not significantly influence lowering MHR and MAP in dippers profile. The effect of reduction of MHR on the non-dipper profile is beneficial for the prognosis of these patients, lowering cardiovascular risk.

Keywords: non-dippers, beta-blockers, high blood pressure, diabetes mellitus, mean heart rate.

Introduction

Ambulatory blood pressure monitoring (ABPM) is the access way to the dippers' status in diabetic hypertensive patients, and it reveals the effects of antihypertensive medication in different dipper

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patterns. Of patients with consecutive type 2 diabetes mellitus (DM) patients with high blood pressure (HBP), 166 were treated with angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta-blockers (βB), calcium channel blockers (CCB), diuretics and different combinations of them, and were subjected to 24 hours' ABPM. We assessed the BP (blood pressure) circadian variation, variability of resting mean heart rate (MHR), and the correlations with the variety of drug combinations. There were 80 non-dippers (48.20%), 22 reverse dippers (13.26%), 57 dippers (34.34%) and 7 extreme-dippers (4.20%).

Non-dippers treated with βB (67.50%) had lower 24 h/MHR – 72.46 bpm *vs.* 78.00 bpm (p=0.015) of those without βB, night MHR – 68.77 bpm *vs.* 73.26 bpm (p=0.038) and day MHR – 74.61 bpm *vs.* 81.50 bpm (p=0.005). Dippers had lowered MAP – 89.77 mmHg and MHR – 71.61 beats per minute (bpm) compared with 91.80 mmHg and 74.26 bpm found in non-dippers (p=0.29; p=0.13). Dippers were treated with ACEI (63.16%), ARB (19.30%), CCB (40.35%), combinations of these (12.28%), βB (59.65%), diuretics (75.44%). The non-dippers diabetics have increased MHR and MAP as compared to dippers, but non-dippers treated with beta-blockers have significantly lower MHR and MAP than those without BB. Treatment of BP with beta-blockers does not significantly influence lowering MHR and MAP in dippers profile.

The effect of reduction of MHR on the non-dipper profile is beneficial for the prognosis of these patients, lowering cardiovascular risk.

The essential advantages of ambulatory blood pressure monitoring (ABPM) are that it can highlight white-coat and masked hypertension, measurement in real-life settings, night-time readings, stronger prognostic evidence, and abundant information from a single measurement session.

ABPM values are, on average, lower than office BP values, and the diagnostic threshold for hypertension is ≥130/80 mmHg over 24h, ≥135/85 mmHg for the daytime average, and ≥120/70 for the night-time average (all equivalent to office BP ≥140/90 mmHg) [1].

Ambulatory blood pressure measurements were a stronger predictor of all-cause and cardiovascular mortality than clinic blood pressure measurements. White-coat hypertension was not benign, and masked hypertension was associated with a greater risk of death than sustained hypertension [2].

Hypertension and diabetes mellitus are two of the significant risk factors for cardio-cerebrovascular diseases (CVDs), although prior studies have confirmed that the coexistence of the two can markedly increase the risk of CVDs [3].

The prevalence of hypertension (HBP) among patients with diabetes mellitus (DM) was twice that of the general U.S. adult population in a 2005–2008 study at 57.3% *versus* 28.6%. Diabetes almost doubles the risk of cardiovascular disease, and concomitant hypertension nearly doubles that risk again [4].

Hypertensive patients with diabetes showed a remarkably high prevalence of alterations in ABPM. Abnormalities in systolic BP, particularly during the night, and in circadian BP patterns could be linked with the excess BP-related cardiorenal risk of diabetes [5].

It is well known that cardiovascular events occur more frequently in the morning as blood pressure (BP) levels have been shown to increase from night to early morning. In recent years, clinical research using home BP monitoring has clarified that morning BP, and BP surges are more closely related to cardiovascular risk than clinical BP [6].

ABPM may also be of particular importance in subjects already under antihypertensive treatment. Even though home BP monitoring may be sufficient for a long-term follow-up, ABPM is the only way to ascertain that BP is adequately controlled all over the 24h period, particularly during the night [7].

High BP is a common feature of both type 1 and 2 diabetes mellitus (T2DM), and masked hypertension is not infrequent, so monitoring 24h ambulatory BP in apparently normotensive patients with diabetes may be a useful diagnostic procedure. Non-dippers with diminished nocturnal blood pressure (BP) and a risers pattern with higher nocturnal BP than daytime are known to have advanced organ damage to the brain, heart, and kidney and poorer prognoses than normal dippers. Non-dipping is frequent in diabetes, and in those patients, ABPM should be performed at least once for the better risk stratification of hypertension [8].

Out-of-office measurement may be useful not only in untreated subjects but also in treated patients, aiming to monitor the effects of treatment and increase compliance with drug therapy [9].

Non-dipping, reverse dipping, nocturnal systolic hypertension (SHT), and masked phenomenon are highly prevalent in patients with T2DM with or without a known history of hypertension. Compared with non-dipping, nocturnal SHT may be a stronger predictor of end-organ damage [10].

Our study investigates the circadian BP variation in hypertensive DM type 2 patients and the effects of hypertension medication. A second point was the assessment of resting 24h heart rate (HR) variability and the correlation with antihypertensive treatment.

Material and methods

Ethics statement

This study was approved by the Ethics Committee of the Emergency County Hospital Baia Mare,

Romania. Written informed consent was obtained from all enrolled patients. Patients' records/information were anonymized and de-identified before the processing.

Study population

One hundred and sixty-six consecutive hypertensive T2DM patients with ambulatory follow-up at the Diabetes and Nutrition Ward of Emergency County Hospital Baia Mare, Romania, were subjected to 24h ABPM from February 2018 to May 2019.

Data collection

General data, weight, waist circumference, height, and body mass index (BMI) details were noted. Before installing the ABPM, values of BP were standardly measured as recommended by the 2013 European Society of Cardiology Hypertension Guidelines [9]. The medical history was recorded for each patient, especially HBP and other cardiovascular diseases (CVD), dyslipidemia, the type of diabetes mellitus, and the recording of its complications – polyneuropathy, nephropathy, peripheral chronic arterial disease (PAD), retinopathy. Each patient had electrocardiography (ECG) done to show any possible left ventricular hypertrophy (LVH) and possible ischemic or rhythm disorders. Current sanguine test results were recorded – glucose, urea, creatinine, total cholesterol, LDL and HDL-cholesterol, triglycerides, uric acid, and glycated hemoglobin (HbA1C). A morning spot sample of urine was collected and checked for the presence of albuminuria and urinary albumin/creatinine ratio (ACR). Microalbuminuria was established as an ACR from 30 to 299 mg/g. For each patient, the antihypertensive and antidiabetic treatment was recorded – beta-blockers (βB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), diuretics (Diur), alpha-blockers (AB), as well as combinations of the above.

ABPM

In this study, a validated BTL-08 ABPM II machine was utilized. The middle values of the systolic and diastolic BP with the differences given by the circadian cycles and the resting HR for each patient were recorded and analyzed: Mean Sys (the systolic mean) and Mean Dias (the diastolic mean), Mean HR – MHR (the heart rate mean), MAP (the mean arterial pressure) and PP (the pulse pressure). To get reliable data on the patient's BP and HR variations, the ABP monitor was worn for 24h, and BP recordings were made at intervals of 0.5 hours from 06.00 to 22.00 hrs and at an hourly interval from 22.00 hrs to 06.00 hrs.

Dippers were defined as those individuals with a mean 24h ambulatory BP lowered >10%. Non-dippers are those individuals with a BP-lowering of 0–9%. Reverse Dippers are those whose dip is less than 0%, and extreme dippers are those individuals whose BP lowering is greater than 20%.

Nocturnal non-dipping of BP is determined according to the nocturnal systolic and diastolic BP dip. Normal ambulatory BP during the day is <135/<85 mm Hg (HBP threshold is 135/85 mmHg) and <120/<70 mm Hg at night (HBP threshold 120/70 mmHg) with a 24h average of <130/80mmHg [8].

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SSPS Inc., Chicago, Illinois, USA) version 20.0 software. Results are summarised as counts and percentages for qualitative variables and as mean±standard deviation (SD) for quantitative variables. Comparisons of means and proportions were made using the student t-test and chi-square test, respectively. A p-value of <0.05 defined the level of statistical significance.

Results

In the study population, out of a total of 166 patients, there were 57 dippers (34.34%), 80 non-dippers (48.20%), 22 reverse dippers (13.26%) and 7 extreme-dippers (4.20%). Epidemiological characteristics correlated to different dipper profiles are shown in Table 1. Non-dippers have higher mean BP, mean albuminuria, and ACR ratio but less uric acid than dippers. Extreme-dippers were eight years younger than other patients and had significantly lower mean BP, mean HbA1 C and uric acid than dippers and non-dippers. Peripheral arterial disease is also less prevalent in this category of patients. History of acute myocardial infarction and higher mean albuminuria and ACR, but less acid uric is more present in reverse dippers compared with dipper patients.

Table 2 shows patients' mean BP values and MHR correlated to different dipper profiles. Dippers had lower MAP/24 h – 89.77 mmHg and MHR – 71.61 beats per minute (bpm) compared with 91.80 mmHg and 74.26 bpm found in non-dippers (p=0.29; p=0.13). MHR/24 h in non-dippers is

Table 1. Epidemiological characteristics correlated to different dipper profiles.

	Total	Non-dipers	Dipers	P_1	Reverse dipers	P_2	Extreme dipers	P_3
Patients: N, (%)	166	80 (48.20)	57 (34.34)	-	22 (13.24)	-	7 (4.22)	-
AGE: years	63.94±9.58	64.07±9.88	64.38±8.94	NS	64.81±7.52	NS	56.14±12.99	0.05
Sex/male N, (%)	77 (46.39)	38 (22.90)	27 (16.27)	NS	10 (6.03)	NS	2 (1.21)	NS
Urban residence N, (%)	98 (59.04)	49 (29.52)	35 (21.09)	NS	11 (6.63)	NS	3 (1.81)	NS
Body mass index (BMI), kg/m^2	34.43±8.05	34.62±9.25	34.17±5.23	NS	35.62±9.31	NS	30.55±5.81	NS
History of AMI N, (%)	25 (15.06)	11 (6.63)	7 (4.22)	NS	7 (4.22)	-	0	NS
Stable angina pectoris: N, (%)	79 (47.59)	37 (22.29)	27 (16.27)	NS	13 (7.84)	NS	2 (1.21)	NS
Heart failure: N, (%)	49 (29.52)	20 (12.05)	20 (12.05)	NS	(4.82)	NS	1 (0.61)	NS
Stroke N, (%)	19 (11.45)	6 (3.62)	9 (5.43)	NS	4 (2.41)	-	0	NS
Peripheral chronic arterial disease N, (%)	60 (36.15)	30 (18.08)	21 (12.65)	NS	7 (4.22)	NS	2 (1.21)	NS
Diabetic polyneuropathy N, (%)	138 (83.14)	63 (37.96)	49 (29.52)	NS	20 (12.05)	NS	6 (3.62)	NS
Diabetic nephropathy N, (%)	70 (42.17)	33 (19.88)	25 (15.06)	NS	8 (4.82)	NS	4 (2.41)	NS
Diabetic retinopathy: N, (%)	40 (24.14)	16 (9.64)	17 (10.24)	NS	6 (3.62)	NS	1 (0.61)	NS
Mean blood glucose (mg%)	250.12±99.73	265.45±106.94	242.87±91.31	NS	236.27±83.36	NS	169.42±59.47	0.021
Mean HbA_1 C (%)	9.73±1.67	9.90±1.64	9.64±1.63	NS	9.79±1.77	NS	8.22±0.70	0.008
Mean total cholesterol (mg/dl))	191.28±51.92	186.04±50.46	200.57±61.23	NS	181.00±29.93	NS	206.82±24.15	NS
Mean serum triglycerides (mg/dl)	209.42±126.57	209.58±133.88	224.31±128.43	NS	159.81±73.08	NS	254.50±115.71	NS
Mean uric acid (mg/dl)	6.48±1.93	6.34±2.20	6.89±1.50	NS	5.90±1.82	NS	6.00±1.36	NS
Mean serum urea (mg/dl)	46.54±22.76	45.71±22.88	46.84±23.95	NS	51.77±19.74	NS	39.15±15.36	NS
Mean serum creatinine (mg/dl)	1.12±0.53	1.09±0.54	1.19±0.56	NS	1.09±0.36	NS	0.92±0.47	NS
Mean microalbuminuria (mg/l)	84.43±131.67	99.37±139.67.	74.53±104.16	NS	63.06±159.22	NS	78.50±99.38	NS
Mean urinary albumin/creatinine ratio (mg/g)	100.09±176.32	113.69±167.87	83.76±136.05	NS	101.56±272.20	NS	70.68±110.21	NS

N – numbers; % – percentage; AMI – acute myocardial infarction; HbA_1 C – glycated haemoglobin; P_1, P_2, P_3 – comparison of dippers, reverse dippers and extreme dippers with non-dippers; NS – non-significant.

Table 2. Mean BP values and mean HR of patients correlated to different dipper profiles.

Mean Holter Values	Total patients (n=166)	Non-Dippers (n=80)	Dippers (n=57)	P_1	Reverse Dippers (n=22)	P_2	Extreme Dippers (n=7)	P_3
Mean Sys/24h	132.01±16.71	132.98±17.50	131.10±17.42	NS	132.45±12.50	NS	126.85±10.81	NS
Mean Dia/24h	70.15±9.91	71.12±9.10	69.17±11.01	NS	69.40±9.98	NS	69.42±7.87	NS
MAP/24h	90.66±10.52	91.80±10.50	89.77±11.84	NS	89.50±6.59	NS	88.57±7.63	NS
Mean HR/24h	73.33±10.55	74.26±9.73	71.61±10.96	0.13	73.04±11.05	NS	77.57±12.08	NS
Pulse Pressure/24h	62.01±13.91	61.81±14.60	61.94±13.32	NS	64.45±13.46	NS	57.14±9.81	NS
Morning Surge	14.97±11.56	12.87±11.08	17.37±12.47	0.027	13.31±7.32	0.86	25.14±11.55	0.0063
Mean Sys Morn	135.71±17.71	136.83±18.21	133.23±18.17	0.25	139.13±15.25	NS	132.00±10.63	NS
Mean Dia Morn	73.95±11.19	75.06±10.58	72.51±12.68	0.20	72.90±9.06	NS	76.00±9.45	NS
MAP Morn	94.50±12.00	95.61±11.71	92.71±13.40	0.18	95.00±9.33	NS	94.57±8.81	HS
Mean HR Morn	74.53±11.86	75.36±11.43	72.67±11.96	0.18	74.31±11.53	NS	80.57±13.70	0.25
Pulse Pressure Morn	61.75±13.97	61.73±14.66	60.73±12.90	NS	66.18±14.16	0.20	56.14±9.06	0.32
Mean Sys Day	133.89±17.27	133.35±17.48	136.64±18.48	NS	127.72±11.83	0.15	137.00±12.98	NS
Mean Dia Day	72.22±10.09	72.53±9.32	73.63±11.49	NS	66.09±6.23	0.002	76.42±8.46	NS
MAP Day	92.77±11.07	92.77±10.62	94.63±12.54	NS	86.63±5.66	0.01	96.85±8.62	NS
Mean HR Day	75.86±11.60	76.85±10.66	74.21±12.15	0.18	74.59±11.63	NS	82.00±13.69	NS
Pulse Pressure Day	61.66±14.07	60.78±14.32	63.07±14.10	NS	61.59±13.34	NS	60.57±12.01	NS
Mean Sys Night	127.62±18.47	130.31±18.74	122.28±16.88	0.011	137.40±15.17	0.10	109.71±9.69	0.005
Mean Dia Night	65.11±9.88	67.31±9.19	61.40±10.17	0.0005	69.45±7.03	NS	56.57±7.34	0.003
MAP Night	85.91±11.27	88.30±10.60	81.64±11.00	0.0005	92.04±7.92	0.12	74.14±7.25	0.0009
Mean HR Night	68.97±9.95	69.91±9.06	66.96±10.29	0.07	70.54±11.08	NS	69.71±10.44	NS
Pulse Pressure Night	62.79±15.33	63.06±16.12	61.61±14.29	NS	68.00±14.66	0.19	53.00±8.24	0.10

BP – blood pressure; HR-mean heart rate; MAP-mean arterial pressure; P_1 comparison of non-dippers *vs.* dippers; P_2 comparison of reverse dippers *vs.* non-dippers; P_3 comparison of extreme dippers *vs.* non-dippers.

significantly higher than in dippers – 74.26 bpm *vs.* 71.61 bpm, p=0.13 and marginally higher than in dippers – day MHR: 76.85 bpm *vs.* 74.21 bpm, p=0.18 and night MHR: 69.91 bpm *vs.* 66.96 bpm, p=0.07. Extreme-dippers, compared with dippers, had lower MAP/24h – 88.57 mmHg *vs.* 89.77 mmHg, and also lower night MAP – 74.14 mm Hg *vs.* 81.64 mmHg, p=0.0009. Day MHR in extreme dippers is higher than in dippers – 82.00 bpm *vs.* 74.21 bpm, and marginally higher for MHR/24 h – 77.57 bpm *vs.* 71.61 bpm.

Reverse dippers, as compared with dippers, have day MAP/24h and night MAP significantly higher (with 4–6 mm Hg), and the night pulse pressure (MHR/24 h) was 68.00 *vs.* 61.61, p=0.19. Day and night MHR in reverse dippers was non-significantly higher (with 2–3 bpm) compared to dippers. MAP night in non-dippers was 88.30 bpm compared to 81.64 bpm in dippers, which was significantly higher (p=0.0005); night MAP was 92.04 in reverse-dipper (p=0.12). Morning surge was low in non-dippers – 12.87 compared to dippers – 17.37 (p=0.027), risers: 13.31 (p=NS) and extreme-dippers: 25.14 (p=0.006).

ACEI were used in 98 patients (59.04%), ARB in 36 patients (21.69%), CCB in 56 patients (33.74%), βB (nebivolol, carvedilol) in 110 patients (66.27%) and diuretics in 124 patients (74.40%).

Non-dippers treated with vasodilating βB (N=54 from 80, 67.50%) had lower 24h MHR – 72.46 bpm *vs.* 78.00 bpm, p=0.015, mornMHR – 73.48 bpm *vs.* 79.26, p=0.032, day MHR – 74.61 bpm *vs.* 81.50, p=0.005 and night MHR – 68.77 bpm *vs.* 73.26 bpm, p=0.038, like those without βB, as shown in Table 3. Non-dippers with βB had significantly lower MAP/24 h – 90.05mmHg *vs.* those without βB – 95.42, p=0.030, MAP morn. – 93.57 mmHg *vs.* 99.84 mmHg, p=0.023, MAP day – 91.12 mmHg *vs.* 96.19 mmHg, p=0.043 and MAP night – 86.59 mmHg *vs.* 91.84 mmHg, p=0.037 (Table 3).

Non-dippers and risers treated with vasodilating βB (N=73 from 102, 71.57%) had lower 24 h MHR – 72.41 bpm *vs.* 78.00 bpm, p=0.010, morn-MHR – 73.60 bpm *vs.* 79.00 bpm, p=0.032, day MHR – 74.24 bpm *vs.* 81.68, p=0.001 and night MHR – 69.20 bpm *vs.* 72.17, p=0.159, like those without βB (Table 4). Non-dippers and risers with βB had significantly lower MAP/24 h – 89.91mmHg *vs.* those without βB – 94.79, p=0.023, MAP morn. – 93.93 mmHg *vs.* 99.37 mmHg, p=0.025, MAP day – 89.90 mmHg *vs.* 95.34 mmHg, p=0.013 and MAP night – 88.12 mmHg *vs.* 91.58 mmHg, p=0.127 (Table 4).

Dippers (N=57) were treated predominantly with ACEI in 36 patients (65.16%), CCB in 23 patients (40.35%), vasodilating βB in 34 patients (59.65%), diuretics in 43 patients (75.44%), ARB in 11 patients (19.30%) and different combinations of these drugs like ACEI/ARB+ CCB in 7 patients (12.28%). Dippers treated with vasodilating βB had lower 24 h MHR – 71.20 βbpm *vs.* 72.21 bpm, day MHR – 73.44 bpm *vs.* 75.34 bpm, and night MHR – 67.41 bpm *vs.* 66.30 bpm, like those without βB (Table 3).

Dippers and extreme dippers treated with vasodilating βB had lower 24h MHR – 72.02 bpm *vs.* 72.59 bpm, day MHR – 74.45 bpm *vs.* 75.88 bpm, and night MHR – 67.97 bpm *vs.* 66.29 bpm, like those without βB (Table 4).

This pattern is also present for the rest of the patients: 3 (42.86%) in extreme dippers (N=7) and 19 (86.37%) in reverse dippers (N=22) were treated with vasodilating βB, and we noted the same HR lowering (4–6 bpm) effect.

Discussion

ABPM is not yet routine in clinical practice in type 2 diabetes. The 2018 European guidelines on treating and managing HBP do not recommend personalized treatment according to circadian hypertensive status. However, they agree that recording 24h ABPM in apparently normotensive people with diabetes may be a useful diagnostic procedure, especially in those with hypertension-mediated damage organs (HMOD) [1, 10]. Nevertheless, different studies contribute to the evidence that supports a personalized treatment approach in the non-dipper BP pattern [11]. Our study demonstrated that non-dipping or reverse dipping of nocturnal BP in people with type 2 DM is a frequent status (48.20% + 13.26% of patients) and is also associated with a higher day, night, and 24 h/MHR as compared to the dippers. Studies from different countries recorded the incidence of BP non-dipping among people with diabetes at 43%, 46%, and 49%, respectively [11–13]. Ambulatory BP monitoring seems to be the only practical way to detect night-time BP [12].

Nocturnal non-dipping of HR predicts future cardiovascular events in hypertensive patients [14]. Thus, ambulatory HR might be considered by the practicing physician as an additional tool for cardiovascular risk stratification [15]. An analysis of prospective studies in patients with HBP found that night-time HR measured by ambulatory recordings was a better predictor of mortality than elevated HR in the clinic. There is convincing evidence that HR is a significant risk factor for cardiovascular disease (CVD) or heart failure (HF). The association is less specific in hypertension without CAD or HF [16]. The measurement of HR adds to the risk stratification for a major adverse cardiovascular event (MACE) and mortality. It shows that an elevated hight-time HR confers an increased mortality risk to hypertensive patients who have normal office HR [17].

There is also evidence of an association in patients with T2D: in 11,140 patients who participated in the

Table 3. Mean HR and MAP of patients dippers and non-dippers, treated with vasodilating βB *vs.* those without βB.

Mean HR Values	Dippers treated with βB (n=34)	Dippers without βB (n=23)	P_1	Non-Dippers treated with βB (n=54)	Non-Dippers without βB (n=26)	P_2
Mean HR/24h	71.20±12.36	72.21±8.43	NS	72.46±10.17	78.00±7.47	0.015
Mean HR Morning	72.45±13.46	73.00±9.40	NS	73.48±11.83	79.26±9.41	0.032
Mean HR Day	73.44±13.56	75.34±9.58	NS	74.61±10.92	81.50±8.35	0.005
Mean HR Night	67.41±11.82	66.30±7.42	NS	68.77±9.53	73.26±7.84	0.040
MAP/24h	89.70±11.84	89.86±11.84	NS	90.05±10.13	95.42±10.34	0.030
MAP Morning	92.39±14.22	93.17±12.10	NS	93.57±11.18	99.84±11.63	0.023
MAP Day	94.47±12.55	94.86±12.54	NS	91.12±10.28	96.19±10.49	0.043
MAP Night	81.76±10.81	81.47±11.28	NS	86.59±10.45	91.84±10.30	0.037

HR – heart rate; N – number; βB – betablockers; p≤0.05. P_1 compares dippers with βB *vs.* dippers without βB; P_2 compars non-dippers with βB *vs.* non-dippers without βB.

Table 4. Mean HR and MAP of patients dippers with extrem-dippers and non-dippers with risers, treated with vasodilating βB *vs.* those without βB.

Mean HR Values	Dippers and Extr. Dippers treated with βB (n=37)	Dippers and Extr. Dippers without βB (n=27)	P_1	Non–Dippers and Risers treated with βB (n=73)	Non-Dippers and Risers without βB (n=29)	P_2
Mean HR/24h	72.02±12.71	72.59±9.33	NS	72.41±10.56	78.00±7.58	0.010
Mean HR Morning	73.33±13.71	73.85±10.98	NS	73.60±11.99	79.00±9.33	0.032
Mean HR Day	74.45±14.09	75.88±10.61	NS	74.24±11.09	81.68±8.76	0.001
Mean HR Night	67.97±11.90	66.29±8.09	NS	69.20±10.18	72.17±7.63	0.159
MAP/24h	89.94±11.63	89.22±11.64	NS	89.91±9.45	94.79±10.25	0.023
MAP Morning	93.13±14.26	92.62±11.58	NS	93.93±10.90	99.37±11.52	0.025
MAP Day	95.00±12.42	94.70±12.35	NS	89.90±9.61	95.34±10.53	0.013
MAP Night	81.32±10.70	80.14±11.56	NS	88.12±10.32	91.58±10.07	0.127

HR – heart rate; N- number; βB – betablockers; p≤0.05. P_1 compares dippers and extreme dippers with βB *vs.* dippers and extreme dippers without βB; P_2 compares non-dippers and risers with βB *vs.* non-dippers and risers without βB.

Action in Diabetes and Vascular Disease – Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study, a higher resting HR rate was associated with a significantly increased risk of all-cause mortality (fully adjusted HR 1.15 per 10 beat/minute [95% CI 1.08, 1.21], P<0.001), cardiovascular death and major cardiovascular outcomes without adjustment and after adjusting for age, sex and multiple covariates. Among patients with diabetes, a higher HR is associated with an increased risk of death and cardiovascular complication [18].

Non-dipping HR was defined as a night/day HR ratio greater than 0.90 in a prospective study where the risk of future CVD was shown to be 2.4 times higher in those whose HR does not exhibit the typical nocturnal decline. The relationship was independent of non-dipping of systolic BP and did not dependent on diabetes status or BP level [19]. At first look, this ratio is not seen in our patients because most of them (66.27%) were already treated with vasodilating βB (Table 2). However, these ratios become evident if we compare the night MHR *vs.* day MHR of dipping (23 patients) and non-dipping patients non-treated with βb (26 pts.): 66.30 bpm/75.34 bpm, and 73.26 bpm/81.50 bpm, respectively. Interestingly, these ratios become lower if we compare the night MHR *vs.* day MHR of dipping (34 pts.) and non-dipping patients treated with βB (54 pts.): 67.41 bpm/73.44 bpm, and 68.77 bpm/74.61 bpm, respectively (Table 3). If we compare these ratios to non-dippers, reverse-dippers *vs.* dippers and extreme dippers remain in the same proportions (Table 4). Our study treated patients with vasodilating βB, such as carvedilol and nebivolol, which have shown neutral or beneficial effects on metabolic parameters in DM hypertensive patients [20, 21].

In June 2015, a panel of experts gathered in a consensus conference to plan updating recommendations on managing the hypertensive patient with elevated heart rate, previously released in 2006. According to the panelists, there is convincing evidence that HR is a significant risk factor for cardiovascular disease. They suggest routinely including HR measurement in the assessment of the hypertensive patient. Regarding the definition of elevated HR, the above-mentioned ESH consensus states that, in the absence of specific data to determine this criterion, any threshold used to define tachycardia is arbitrary, but a value of at least 80 bpm is compatible with published data [22].

In this context, the importance of our study is to add evidence about the importance of measuring HR in DM hypertensive patients and suggest a possible approach by using vasodilating βB. Higher HR may impair the prognosis and should also be routinely assessed, especially in non-dipper, reverse dipper, and extreme dipper patients, which our study shows to be more frequent.

In our study, in dipper patients with βB *vs.* those without βB, the Mean HR/24 h decrease was not so significant – 71.20 bpm *vs.* 72.21 bpm. In contrast to non-dippers treated with βB *vs.* those without βB, the decrease of Mean HR/24 h was significant: 72.46 bpm *vs.* 78.00 bpm, p=0.015; Mean HR day of non-dippers with βB *vs.* those without βB were 74.61 bpm *vs.* 81.50 bpm, p=0.005 and Mean night HR of dippers with βB *vs.* those without βB were 68.77 bpm *vs.* 73.26 bpm, p=0.038. There is the same trend comparing the non-dippers and reverse-dippers group with beta-blockers *versus* those without βB: Mean HR/24h: 72.41 bpm *vs.* 78.00 bpm, p=0.010, Mean day HR: 73.60 bpm *vs.* 79.00 bpm, p=0.032 and Mean night HR was 69.20 bpm *vs.* 72.17 bpm, p=0.159.

Reduced diurnal blood pressure variation in non-insulin-dependent diabetic patients with microalbuminuria is associated with an increased prevalence of target organ damage [23]. In our study, the median urinary albumin excretion in non-dippers: 99.37 mg/24h was greater than in dippers: 74.53 mg/24h, p=0.26; these facts suggest that in non-dipper hypertensive patients, the presence of greater renal damage than in dippers [24]. Albuminuria is strongly associated with the non-dipping of nocturnal BP in people with type 2 diabetes [25].

The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the prevention, detection, evaluation and management of HBP in adults and the 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines for the management of BP, both recommend restricted use of beta-blockers as first-line therapy [26]. However, our study shows the importance of beta-blocker treatment in the non-dipper profile of diabetic hypertensive patients, associated profile and increased risk of CV events, and more frequent complications of DM and HBP.

Further clinical studies are needed to provide evidence to support the optimum HR to be achieved and to evaluate if the effects of HR reduction in hypertensive patients with elevated HR (≥80 bpm) have long-term benefits. Our study shows that ABPM is a potential method that could also be used to determine the optimum HR to be achieved and/or the HR threshold at which treatment should be started, especially in those with high CV risk, like DM-hypertensive patients. Although in need of further confirmation in larger studies, our findings highlight a potential opportunity to improve current prescription practices of beta-blockers in patients with DM, especially in non-dipper patterns.

Our study shows the association of microalbuminuria and a higher ACR with the non-dipping and reverse dipping status. These results are in accordance with previous research that has shown a significant correlation between the presence of nocturnal non-dipping of BP and increased levels of urinary albumin excretion; reduced diurnal blood pressure variation is associated with an increased

prevalence of target organ damage. However, this was not an objective of our study, and we did not proceed to further correlations with age, weight, lipid profile, DM duration, or intensity of antidiabetics and glycaemic control, and ischemic heart disease.

Limitations of the study

There are few studies to report the association of a higher HR with non-dipper and reverse-dipper patterns of BP in T2DM patients.

Meanwhile, we only investigated the circadian BP pattern, whereas, for a larger number of patients, a better description and identification of possible confounders and multiple ABPM over a more extended period may provide more prognostic information about the importance of nocturnal non-dipping of HR in diabetic hypertensive patients.

Conclusions

The current study has shown that non-dipping or reverse dipping of nocturnal BP in patients with type 2 DM has a frequent status (over 60% of them). Most of them also have a higher resting HR than dipper patients, which may affect the long-term prognosis. ABPM should be carried out in every hypertensive diabetic patient to identify dipper/no dipper status. Including HR measurement in the clinical assessment is required, but further research should clarify the importance of HR lowering in DM type 2 hypertensives patients. In the end, this study underlines the importance of beta-blocker treatment in diabetic hypertensive patients, especially in the non-dipper profile present in about 50% of cases, *i.e.*, profiles associated with comorbidities and increased cardiovascular risk. This treatment is proving its effectiveness along with other antihypertensive agents.

Conflict of Interest

The authors confirm that there are no conflicts of interest.

References

1. Williams B, Mancia G, Spiering E, Agabiti Rosei E, Azizi M et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). European Heart Journal. 2018; 39: 3021-3104.
2. Banegas JR, Ruilope LM, de la Sierra A, Vinyoles E, Gorostidi M, et al, Relationship between clinic and ambulatory blood-pressure measurements and mortality. N Engl J Med. 2018; 378 (16): 1509-1520.
3. Wang et al. Prevalence of diabetes and hypertension and their interaction effects on cardio-cerebrovascular diseases: a cross-sectional study. BMC Public Health (2021) 21: 1224.
4. Mc Farlane SI, Bakris GL. Diabetes and Hypertension: Evaluation and Management. Humana Press. 2012; doi 10.1007/978-1-60327-357-2.
5. Gorostidi M, de la Sierra A, Gonzalez-Albarran O, Segura J, de la Cruz JJ, et al : Abnormalities in ambulatory blood pressure monitoring in hypertensive patients with diabetes. Hypertension Research. 2011; 34:1185-1189.
6. Kazoumi K. Essential Manual of 24 Hour Blood Pressure Management: From Morning to Nocturnal Hypertension. John Wiley &Sons, Ltd.2015; ISBN: 9781119087243, Chapter 3, 35-49.
7. Parati G, Bilo G. Should 24-h Ambulatory Blood Pressure Monitoring Be Done in Every Patient With Diabetes?. Diabetes Care. 2009: 32(2):298-304.
8. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, et al. 2013 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). J Hypertens. 2013; 31(7): 1281-1357.
9. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, et al 2016 European Guidelines on cardiovascular disease prevention in clinical practice. The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016; 37: 2315-2381.
10. Florence Gunawan, Hui Yi Ng, Cristopher Gilfillan and Mahesan Anpalahan. Ambulatory Blood pressure Monitoring in Type 2 Diabetes mellitus: A Cross-sectional Study. Current Hypertension Reviews. ISSN(Print):1573-4021, ISSN(Online):1875-6506, Volume15, Issue 2, 2019, Page:[135-143].
11. Mahabala C, Kamath P, Bhlaskaran U, Pai ND, Pai AU. Antihypertensive therapy: nocturnal dippers and nondippers. Do we treat them differently? Vasc Health Risk manag. 2013; 9: 125-133.
12. Verdecchia P, Porcelatti C, Schiallaci G, Borgioni C, Ciucci A, et al. Ambulatory blood pressure : an independent predictor of prognosis in essential hypertension. Hypertension. 1994; 24: 793-801.
13. Duggal A, Bal BS, Singh N. Study of dipping and non-dipping patterns in patients of type 2 diabetes mellitus

with hypertension and its association with microalbuminuria. Ann Int Med Den Res. 2017; 3(2):20-24.
14. Sturrock ND, George E, Pound N, Stevenson J, Peck GM, Sowter H. Nondipping circadian blood pressure and renal impairment associated with increased mortality in diabetes mellitus. Diabet Med 2000; 17:360-364.
15. Palatini P, Reboldi G, Beilin LJ, Eguchi K, Ymai Y, et al.Predictive value of night-time heart rate for cardiovascular events in hypertension. The ABP- International study. Int J Cardiol. 2013; 168(2): 1490-1495.
16. Tomlinson B, Sritara P,Lopez E, Dalal J, Erwinanto E, Pancholia AK. Hypertension and elevated heart rate: focus on the Asia Pacific region. J Hypertens. 2016; 34: 2330-2332.
17. Palatini P, Reboldi G, Beilin LJ, Casiglia E, Eguchi K, et al. Masked tachycardia. A predictor of adverse outcome in hypertension. J Hypertens. 2017; 35: 487-492.
18. Hillis GS, Woodward M, Rodgers A, Chow CK, Li Q, et al. Resting heart rate and the risk of death and cardiovascular complications in patients with type 2 diabetes mellitus. Diabetologia. 2012; 55: 1283-1290.
19. Eguchi K, Hoshide S, Ishikawa J, Pickering TG, Schwartz JE, et al. Nocturnal nondipping of heart rate predicts cardiovascular events in hypertensive patients. J Hypertens, 2009; 27(11): 2265-2270.
20. Arnold SV, Spertus JA, Lipska KJ, Lanfear DE, Tang F, et al. Type of β-blocker use among patients with *versus* without diabetes after myocardial infarction. American Heart J. 2014; 168(3): 273-279.
21. Fergus IV, Connell KL, Ferdinand KC. A Comparison of Vasodilating and Non-vasodilating Beta-Blockers and Their Effects on Cardiometabolic Risk. Curr Cardiol Rep. 2015; 17: 38. https://doi.org/10.1007/s11886-015-0592.
22. Palatini P, Rosei EA, Casiglia E, Chalmers J, Ferrari R, et al. Management of the hypertensive patient with elevated heart rate: Statement of the Second Consensus Conference endorsed by the European Society of Hypertension. J Hypertens. 2016; 34:813-821.
23. Lindsay RS, Stewart MJ, Nairn IM, Baird JD, Padfield PL. Reduced diurnal variation of blood pressure in non-insulinodependent diabetic patients with microalbuminuria. J Hum Hypertens. 1995; 9: 223-227.
24. Bianchi S, Bigazzi R, Baldari G, Sgherri G, Campese VM. Diurnal variations of blood pressure and microalbuminuria in essential hypertension. Am J Hypertens. 1994; 7: 23-29.
25. Sommerfield AJ, Robinson L, Padfield PL, Strachan MW. Clinical variables associated with non dipping of nocturnal bloob pressure in type 2 diabetes. Br J Diabetes Vasc Dis. 2008; 8: 236-240.
26. Bakris G, Waleed Ali, Parati G, ACC/AHA *versus* ESC/ESH on Hypertension Guidelines-JACC Guideline Comparason, JACC vol.73.No.23, 2019, June 18.2019: 3018-26.