




## ORIGINAL ARTICLE

# Prognostic value of 24-hour ambulatory blood pressure patterns in diabetes: A 21-year longitudinal study

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## Abstract

**Aims:** To establish the long-term prognostic value of abnormal circadian blood pressure (BP) patterns in diabetes.

**Materials and Methods:** We retrospectively examined a cohort of 349 outpatients with diabetes who were screened for microvascular complications and followed up for 21 years. Dipping, nondipping and reverse-dipping status were defined based on 24-hour ambulatory BP monitoring (ABPM) as  $\geq 10\%$  reduction,  $< 10\%$  reduction, and any increase in average nighttime versus daytime systolic BP (SBP), respectively.

**Results:** After 6251 person-years of follow-up (median [range] follow-up 21.0 [1.1–22.0] years, 52% women, age  $57.1 \pm 11.9$  years, 81.4% type 2 diabetes and 18.6% type 1 diabetes), a total of 136 deaths (39%) occurred. Compared with dippers, the nondippers and reverse dippers showed progressively higher prevalence of chronic kidney disease (CKD), cardiac autonomic neuropathy (CAN) and postural hypotension. Reverse dippers showed a 13.4% (2.5-year) reduction in mean overall survival and a twofold increased risk of all-cause mortality after adjustment for traditional risk factors (hazard ratio 2.2 [95% confidence interval 1.3–3.8]). Each 1% decrease in nighttime versus daytime SBP ratio was independently associated with a 4% reduction in 20-year mortality risk.

**Conclusions:** In patients with diabetes, reverse dipping is associated with a higher prevalence of CKD and CAN and more than doubled the adjusted risk of all-cause mortality over a 21-year observation.

## KEYWORDS

cardiovascular disease, diabetic neuropathy, type 1 diabetes, type 2 diabetes, observational study, diabetes complications

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## 1 | INTRODUCTION

Abnormal circadian blood pressure (BP) patterns are established risk factors for cardiovascular events in people with diabetes<sup>1</sup> and in the general population.<sup>2,3</sup> A reduction in the physiological fall in nighttime systolic BP (SBP) values, defined as “nondipping” (nocturnal SBP fall <10% of the daytime SBP value), is highly prevalent in type 1<sup>4</sup> and type 2 diabetes,<sup>5</sup> and is associated with resistant hypertension,<sup>6</sup> hypertension-mediated target organ damage,<sup>7</sup> endothelial dysfunction,<sup>8</sup> and carotid atherosclerosis.<sup>9</sup>

In subjects without diabetes, a nondipping nocturnal pattern of BP has been independently correlated with cardiovascular disease (CVD),<sup>2,10</sup> heart failure,<sup>11</sup> and increased mortality.<sup>7,12</sup> In patients with diabetes, it has been associated with poor metabolic control<sup>13</sup> and adverse cardiorenal outcomes, including progression of diabetic kidney disease (DKD) in type 1 diabetes,<sup>14</sup> and microalbuminuria and cardiac autonomic neuropathy (CAN) in both type 1 diabetes and type 2 diabetes.<sup>15-18</sup> Although the associations of abnormal BP dipping with diabetes complications and CVD have been extensively explored in cross-sectional studies, longitudinal studies are scarce and have short follow-up periods (no longer than 10 years).<sup>16,19-22</sup> Moreover, “reverse dippers” (also called “risers” or “inverted dippers”), who have a mean nocturnal BP higher than diurnal BP (nighttime/daytime SBP ratio >1), have been assessed separately from nondippers in only a few studies.<sup>19,21-23</sup> This is of particular interest since recent evidence has shown that reverse dippers are characterized by more severe hypertension-mediated organ damage and increased risk of CVD and Alzheimer's disease in the general population and of lower limb events in patients with type 2 diabetes.<sup>23-26</sup>

The aim of the present study was to define the clinical features and long-term prognostic value for all-cause mortality of the different BP patterns, as measured through 24-hour ambulatory BP monitoring (ABPM), in patients with diabetes. To this end, we retrospectively analysed cross-sectional and 21-year longitudinal data from the “CHronic diabetes complications and All-cause Mortality in Pisa from 1999 Onwards” (CHAMP1ON) study cohort, including 497 participants who underwent 24-hour ABPM, comprehensive clinical and metabolic profiling, and direct characterization of diabetes microvascular complications, including DKD, neuropathy and retinopathy.

## 2 | METHODS

### 2.1 | Study population

We retrospectively analysed data from a total of 497 consecutive outpatients attending the Section of Dietology and the Units of Internal Medicine 1 and 3 of the University Hospital of Pisa between 1999 and 2000, who were recruited into the CHAMP1ON study cohort. Men and women, aged between 18 and 75 years, with a history of diabetes or prediabetes (either impaired fasting glucose or impaired glucose tolerance) were eligible for inclusion. Most patients presented with multiple common pathological conditions associated with

diabetes, including hypertension, obesity and dyslipidaemia, which are characteristics of the metabolic syndrome. Exclusion criteria were concomitant acute or chronic diseases associated with reductions in life expectancy, including lung, hepatic, neoplastic or inflammatory diseases, end-stage chronic kidney disease (CKD), CV events in the previous 12 months and working nightshifts.

At the time of recruitment, a full clinical history was obtained. Demographic data, anthropometric variables, medication, and family history of hypertension and diabetes were also recorded. All participants underwent a physical examination by a trained physician and a comprehensive clinical and biochemical characterization, including blood and urine sampling for the determination of routine chemistry, metabolic profiling, and inflammatory markers. The diagnosis of diabetes was made in accordance with the 1997 American Diabetes Association Standards of Medical Care for Patients with Diabetes Mellitus (ie, fasting plasma glucose >7.0 mmol/L, plasma glucose >11.1 mmol/L and classic symptoms of diabetes, 2-hour plasma glucose >11.1 mmol/L during an oral glucose tolerance test).<sup>27</sup> Patients with diabetes were screened for the presence of major microvascular complications, including neuropathy, nephropathy and retinopathy. Participants with resistant hypertension or a clinical suspicion for secondary hypertension were screened for causes of secondary hypertension and.<sup>28</sup> All participants were treated according to the best clinical practice in effect at that time and periodically attended the clinic in relation to their clinical needs.

The vital status of study subjects was verified in April 2021 by interrogating the Italian Health Care database, which provides updated information on all current Italian residents. For the present analysis, we included only patients with diabetes and available 24-hour ABPM and survival data.

The study was approved by the local Human Ethics Committee and conducted in accordance with the principles expressed in the Declaration of Helsinki. All subjects provided written informed consent before enrolment.

### 2.2 | BP measurements

Office BP was obtained by averaging three consecutive measurements taken during the enrolment visit and spaced by 5-minute intervals. BP was taken with a mercury sphygmomanometer using appropriate cuff sizes. Patients rested for at least 5 minutes before the BP measurements were taken and abstained from physical exercise, eating or smoking for at least 30 minutes before. In-office hypertension was defined as SBP  $\geq$ 140 mmHg and/or diastolic BP (DBP)  $\geq$ 90 mmHg.<sup>28</sup>

The ABPM recordings were performed at the time of enrolment while patients continued their antihypertensive treatment, if any, using an oscillometric BP monitor (Takeda TM3420, Tokyo, Japan) with adequate cuff size. BP readings were taken every 15 minutes during the day from 7:00 AM to 10:00 PM and every 30 minutes during the night from 10:00 PM to 07:00 AM, which approximately coincided with resting and sleeping time. The ABPM reading was considered

acceptable if at least 70% of the BP recordings were deemed as valid.<sup>28</sup>

Dipping, nondipping and reverse dipping were defined, respectively, as a  $\geq 10\%$  decline,  $< 10\%$  decline, and any increase in average nighttime SBP compared with average daytime SBP, as indicated by the European Society of Hypertension (ESH) guidelines.<sup>29,30</sup>

In accordance with the current European Society of Cardiology/ESH guidelines for the management of arterial hypertension,<sup>28</sup> patients were classified as hypertensive if they showed any one of the following criteria: SBP  $\geq 130$  mmHg and/or DBP  $\geq 80$  mmHg during 24-hour ABPM recording, SBP  $\geq 135$  mmHg and/or DBP  $\geq 85$  mmHg during daytime ABPM recording, SBP  $\geq 120$  mmHg and/or DBP  $\geq 70$  mmHg during nighttime ABPM recording, or treatment with at least one antihypertensive drug. Patients were further classified as having controlled hypertension if they were on any BP-lowering drug and had ABPM values below the upper limits of normal mentioned above, or as having uncontrolled hypertension if they had ABPM values above the upper normal limits irrespective of treatment.<sup>28,29</sup> Isolated nocturnal hypertension was defined as average nighttime SBP  $> 120$  mmHg in the presence of controlled diurnal, 24-hour and office BP values.<sup>29</sup>

### 2.3 | Echocardiography

All patients underwent a comprehensive transthoracic echocardiography examination at rest. Data collected included: left ventricle thickness, volumes, geometry, and ejection fraction; left ventricle volumes and ejection fraction were calculated from the apical two- and four-chamber views using the modified Simpson's rule. Left ventricle hypertrophy was defined as a left ventricle mass/body surface area  $> 115$  g/m<sup>2</sup> in men and  $> 95$  g/m<sup>2</sup> in women. Concentric remodelling was defined as a relative wall thickness  $\geq 0.43$ .<sup>28</sup>

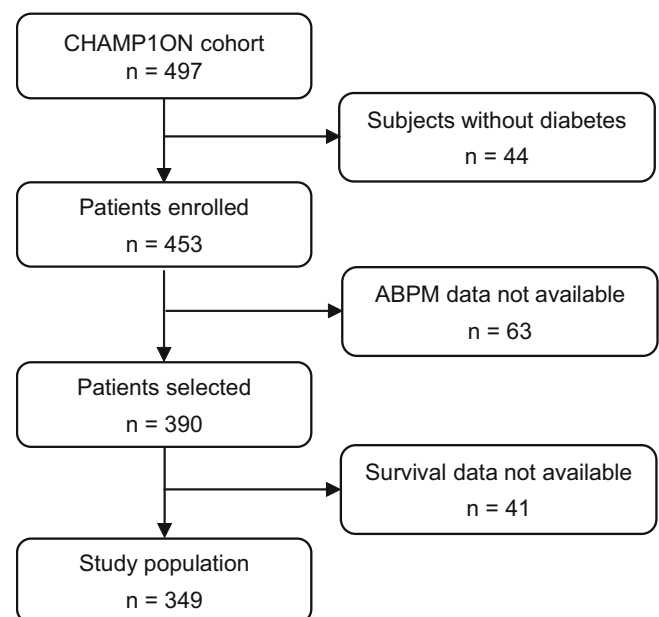
### 2.4 | Microvascular complications assessment

Nephropathy was assessed by determining estimated glomerular filtration rate (eGFR) with the Modification of Diet in Renal Disease (MDRD) equation and by measuring overnight albumin excretion rate (AER). Microalbuminuria was defined as AER 20 to 200  $\mu\text{g}/\text{min}$  and macroalbuminuria as AER  $\geq 200$   $\mu\text{g}/\text{min}$ .<sup>31</sup> Creatinine and AER values were available for 320 and 299 patients, respectively. A total of 248 patients underwent fundoscopic examination for the detection of diabetic retinopathy, which was staged in background, preproliferative or proliferative diabetic retinopathy in accordance with American Diabetes Association's criteria.<sup>32</sup> The presence of CAN was determined in 205 patients through a battery of cardiovascular tests using a portable computerized system (Cardionomic, Medimatica, Martinsicuro,

Italy). CAN was diagnosed if patients had at least two tests among lying-to-standing, standing-to-lying, and deep breathing tests showing reduced heart rate variability and/or orthostatic hypotension, defined as a reduction  $\geq 20$  mmHg in SBP within 3 minutes of standing.<sup>28,33</sup> The presence of peripheral neuropathy was screened through the monofilament test and confirmed through electroneurography in 230 patients.

### 2.5 | Statistical analyses

Continuous normally distributed variables are presented as mean  $\pm$  SD and non-normally distributed variables are presented as median (interquartile range). Differences between groups were tested using the chi-squared test for nominal variables and ANOVA or the Kruskal-Wallis test for normally or non-normally distributed continuous variables, respectively. The Cochran-Armitage test was used to detect linear trends for dichotomic variables. Kaplan-Meier curves were compared using the log-rank test and graphically compared to the corresponding model-derived curves for risk prediction. The Cox proportional hazards model was used to determine the hazard ratio (HR) and 95% confidence interval (CI) for all-cause mortality. The proportional hazards assumption was tested for each model by conducting a global analysis for each adjusted model, and *P* value for the whole test was  $< 0.0001$  for all the models. Overall survival was calculated as the time between the ascertained time of death and the date of enrolment. Multivariate Model 1 was adjusted for age, sex, body mass index (BMI), glycaemic control (glycated haemoglobin [HbA1c]  $\geq 58$  mmol/mol vs. HbA1c  $< 58$  mmol/mol), eGFR (MDRD equation), type and duration of diabetes and office SBP. To exclude the mediating effect of higher 24-hour or nocturnal BP values on the influence of circadian



**FIGURE 1** Flow diagram showing patient selection. ABPM, ambulatory blood pressure monitoring

**TABLE 1** Baseline characteristics of study participants stratified by dipping patterns

Characteristics	Dippers (n = 166)	Nondippers (n = 144)	Reverse dippers (n = 39)
Age, years	57 (63-50)	60 (52-59)	63 (55-68) <sup>a</sup>
Women, %	55	47	64
BMI, kg/m <sup>2</sup>	28 (25-32)	29 (25-35)	29 (25-35)
<b>Diabetes type</b>			
Type 1 diabetes, %	21	18	13
Type 2 diabetes, %	79	82	87
Duration of diabetes, years	10 (4-19)	10 (4-21)	10 (5-21)
<b>Smoking</b>			
Active smokers, %	35	31	23
Ex-smokers, %	20	22	23
Family history of hypertension, %	30	33	41
Family history of diabetes, %	39	46	54
<b>Metabolic characteristics</b>			
HbA1c, mmol/mol	67 (53-83)	67 (55-84)	74 (62-97)
Fasting plasma glucose, mmol/L	8.6 (6.9-11.4)	8.8 (7.1-10.9)	8.9 (6.7-11.7)
Total cholesterol, mmol/L	5.4 (4.7-6.2)	5.6 (4.8-6.4)	5.2 (4.6-6.0)
HDL cholesterol, mmol/L	1.2 (1.0-1.4)	1.2 (1.0-1.4)	1.2 (1.0-1.3)
LDL cholesterol, mmol/L	4.6 (4.0-5.3)	4.6 (4.1-5.4)	4.4 (3.8-5.4)
Triacylglycerol, mmol/L	1.5 (1.4-1.7)	1.7 (1.2-2.3)	1.6 (1.3-2.2)
Lipoprotein (a), nmol/L	22 (16-59)	22 (16-72)	22 (16-77)
Apo A1, mg/dL μmol/L	50 (45-54)	49 (42-57)	50 (39-57)
Apo B, μmol/L	2.1 (1.7-2.4)	2.2 (1.9-2.5)	2.0 (1.7-2.5)
<b>Inflammatory markers</b>			
Homocysteine, μmol/L	9.1 (8.0-12.8)	9.9 (8.1-12.5)	11.0 (8.7-13.2)
Urate, mg/dL	5.0 (4.2-6.5)	5.5 (4.3-6.8)	5.7 (4.9-6.2)
Fibrinogen, mg/dL	373 (320-435)	373 (319-443)	381 (320-410)
Ferritin, mg/dL	105 (40-225)	74 (62-113)	105 (40-225)
ESR, mm/2 h	26 (19-45)	32 (21-42)	34 (26-50)
CRP, mg/dL	0.4 (0.3-0.7)	0.4 (0.4-1.2)	0.4 (0.3-1.0)
<b>Blood pressure</b>			
Hypertension, %	71	90 <sup>a</sup>	95 <sup>a</sup>
Controlled hypertension, %	11	8	3
Uncontrolled hypertension, %	60	82 <sup>a</sup>	92 <sup>a</sup>
Office SBP, mmHg	140 (126-159)	140 (130-157)	150 (135-160)
Office DBP, mmHg	86 (80-92)	85 (79-90)	82 (76-90)
Mean 24-h SBP, mmHg	126 (115-134)	134 (125-142) <sup>a</sup>	137 (123-148) <sup>a</sup>
Mean 24-h DBP, mmHg	74 (68-78)	76 (70-81) <sup>a</sup>	75 (70-81)
Mean daytime SBP, mmHg	136 (124-145)	137 (128-146)	134 (120-144)
Mean daytime DBP, mmHg	80 (74-85)	79 (74-84)	76 (71-81) <sup>a</sup>
Mean nighttime SBP, mmHg	115 (105-125)	130 (121-139) <sup>a</sup>	141 (124-152) <sup>a,b</sup>
Mean nighttime DBP, mmHg	68 (61-72)	73 (67-79) <sup>a</sup>	75 (70-83) <sup>a</sup>
Masked hypertension, %	11	19	18 <sup>c</sup>
White-coat hypertension, %	14	7	5 <sup>c</sup>
<b>Medications</b>			
N° of antihypertensive drugs			
None, %	50	30 <sup>a</sup>	19 <sup>a</sup>
1, %	24	29	38
2, %	15	27	15

TABLE 1 (Continued)

Characteristics	Dippers (n = 166)	Nondippers (n = 144)	Reverse dippers (n = 39)
≥ 3, %	11	14	28
ACE inhibitors, %	35	47	49
AT1-receptor blockers, %	2	0	0
Beta blockers, %	6	6	10
Ca-antagonists, %	18	23 <sup>a</sup>	31 <sup>a</sup>
Alpha1-antagonists, %	9	10 <sup>a</sup>	23 <sup>a</sup>
Alpha2-agonists, %	1	5	3
Diuretics, %	8	16	10
Statins, %	7	10	8
Oral antidiabetic drugs, %	49	41	41
Insulin therapy, %	33	35	31
Insulin total daily dose, IU	40 (32-48)	40 (30-48)	32 (25-40)
<b>Echocardiographic measures</b>			
Ejection fraction, %	60 (60-64)	60 (58-62)	60 (60-63)
Interventricular septum, mm	11.0 (10.0-12.5)	12.0 (11.0-13.0)	12.0 (11.0-13.0)
Left ventricular mass index, g/m <sup>2</sup>	115 (99-129)	117 (105-134)	129 (109-145)
Relative Wall thickness, ratio	0.44 (0.42-0.48)	0.43 (0.42-0.47)	0.47 (0.43-0.51) <sup>b</sup>
Left ventricular remodelling			
Eccentric, %	32	35	12 <sup>a</sup>
Concentric, %	68	65	88 <sup>a</sup>
<b>Microvascular complications</b>			
eGFR, mL/min/1.73 m <sup>2</sup> (MDRD equation)	78 (69-92)	81 (68-102)	80 (91-91)
eGFR, mL/min/1.73 m <sup>2</sup> (CKD-EPI equation)	78 (69-96)	84 (68-98)	82 (60-95)
CKD stage			
I-II, %	91	86	78
III-IV, %	9	14	22 <sup>c</sup>
Albuminuria			
No albuminuria, %	82	79	71
Microalbuminuria, %	14	17	23
Macroalbuminuria, %	4	4	6
Retinopathy			
No retinopathy, %	65	65	50
Background retinopathy, %	22	15	34
Preproliferative retinopathy, %	13	17	13
Proliferative retinopathy, %	0	3	3
Cardiac autonomic neuropathy, %			
Deep breathing Δexp/insp HR, ratio	1.2 (1.1-1.3)	1.2 (1.1-1.3)	1.2 (1.1-1.3)
Lying to standing ΔHR, ratio	1.2 (1.1-1.3)	1.2 (1.1-1.3)	1.1 (1.1-1.2)
Standing to lying ΔHR, ratio	1.1 (1.1-1.2)	1.1 (1.1-1.2)	1.1 (1.2-1.1)
Postural dip in SBP, mmHg	18 (8-26)	21 (14-29) <sup>a</sup>	24 (18-39) <sup>a</sup>
Peripheral neuropathy, %	23	21	16

Note: Data are presented as median (interquartile range) or percentage. Differences were tested using chi-squared or Kruskal-Wallis tests, followed by post hoc pairwise comparisons as appropriate. The Cochran-Armitage test was used to detect linear trends for dichotomic variables.

<sup>a</sup>P < 0.05 vs. dippers.

<sup>b</sup>P < 0.05 vs. non-dippers.

<sup>c</sup>P < 0.05 for trend across groups.

Abbreviations: ACE, angiotensin-converting enzyme; Apo, apolipoprotein; AT-1, angiotensin II type 1; BMI, body mass index; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; exp, expiration; HbA1c, glycated haemoglobin; HR, hazard ratio; insp, inspiration; MDRD, Modification of Diet in Renal Disease; SBP, systolic blood pressure.

dipping patterns on all-cause mortality, Models 2 and 3 also included adjustments for 24-hour BP control (SBP  $\geq 130$  mmHg and/or DBP  $\geq 80$  mmHg vs. SBP  $< 130$  mmHg and DBP  $< 80$  mmHg during 24-hour ABPM), and isolated nocturnal hypertension, respectively, instead of office SBP. To examine the influence of the intensity of antihypertensive treatment, Model 4 included the number of antihypertensive medications in addition to all the covariates of Model 1. Using continuous rather than categorical variables as covariates (ie, HbA1c, 24-hour SBP, 24-hour DBP) would not affect study findings. As all multivariate models included the type of diabetes as a covariate, we did not conduct separate analyses for type 1 diabetes and type 2 diabetes. The effects of diabetes type and age were further examined by adding an interaction term between type of diabetes or age and the variable of interest in all adjusted models.

Prediction profilers in JMP Pro software version 16.0.0 (SAS Institute Inc., Cary, North Carolina) were used to display the conditional relationship between nocturnal BP percent dipping and all-cause mortality risk at 10 or 20 years of follow-up in the whole cohort and in two representative patients (50-year-old man or woman).

Statistical analyses were performed using SPSS Statistics software version 22.0 (IBM Corp., Armonk, New York) and JMP Pro software version 16.0 (SAS Institute Inc.) at a two-sided  $\alpha$ -level of 0.05.

### 3 | RESULTS

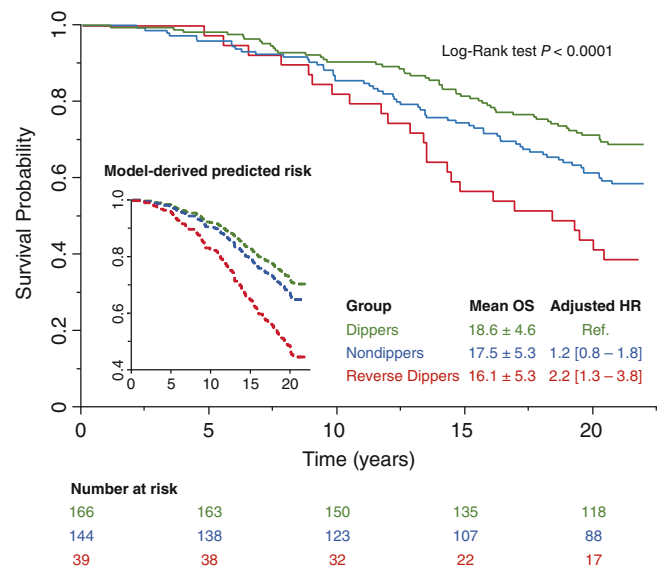
#### 3.1 | Study population

The study population consisted of 349 subjects (Figure 1), including 284 patients (81.4%) with type 2 diabetes and 65 (18.6%) patients with type 1 diabetes (age  $57.1 \pm 11.9$  years, BMI  $29.4 \pm 5.9$  kg/m<sup>2</sup>, HbA1c  $70 \pm 17$  mmol/mol). Women and men were evenly represented. Most patients had hypertension (82%), with uncontrolled hypertension occurring in 73% of cases.

#### 3.2 | Characteristics of nondipping and reverse-dipping patients

Clinical and metabolic characteristics of the study population stratified by dipping patterns are presented in Table 1. The number of dippers, nondippers and reverse dippers was 166 (48%), 144 (41%), and 39 (11%), respectively. The reverse dippers were older than dippers; all other clinical and metabolic characteristics were similar among the subgroups.

Hypertension, uncontrolled hypertension, and masked hypertension were more prevalent in nondippers and reverse dippers than in dippers, while white-coat hypertension was less frequent (Table 1). In fact, compared with dippers, reverse dippers had significantly higher 24-hour SBP and mean daytime DBP, and both reverse dippers and nondippers showed higher nighttime SBP and DBP and were more likely to be treated with antihypertensive agents. The prevalence of



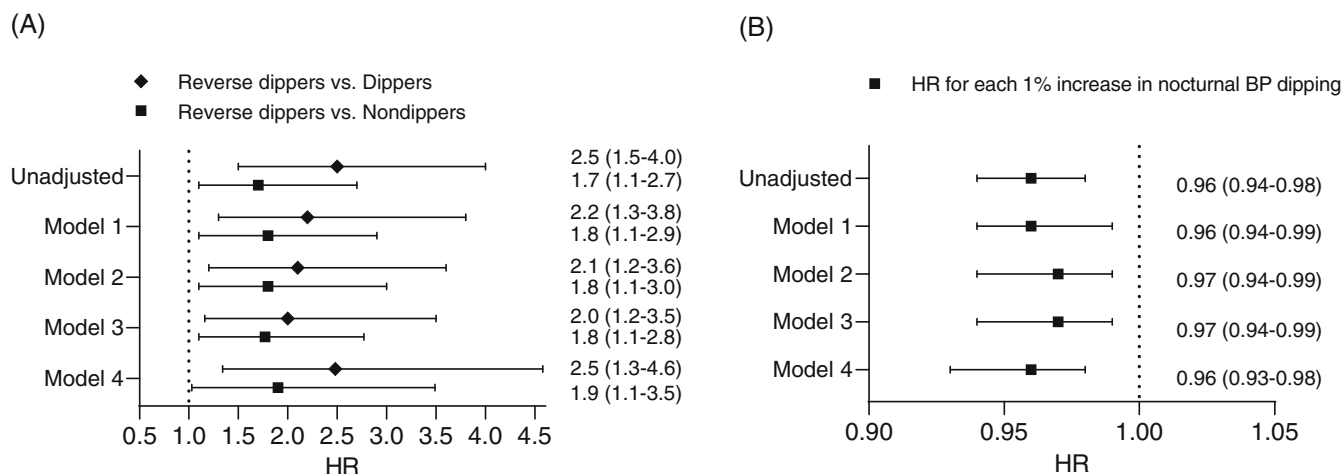
**FIGURE 2** Kaplan-Meier and model-predicted survival curves for nocturnal blood pressure (BP) dipping groups. Kaplan-Meier curves were compared with the log-rank test. The Cox proportional hazards model was used to determine the hazard ratio (HR) for all-cause mortality including age, sex, body mass index, glycaemic control, estimated glomerular filtration rate, type and duration of diabetes, and office systolic blood pressure as covariates. OS, overall survival

white-coat hypertension decreased across the three dipping groups, with the highest occurrence among dippers.

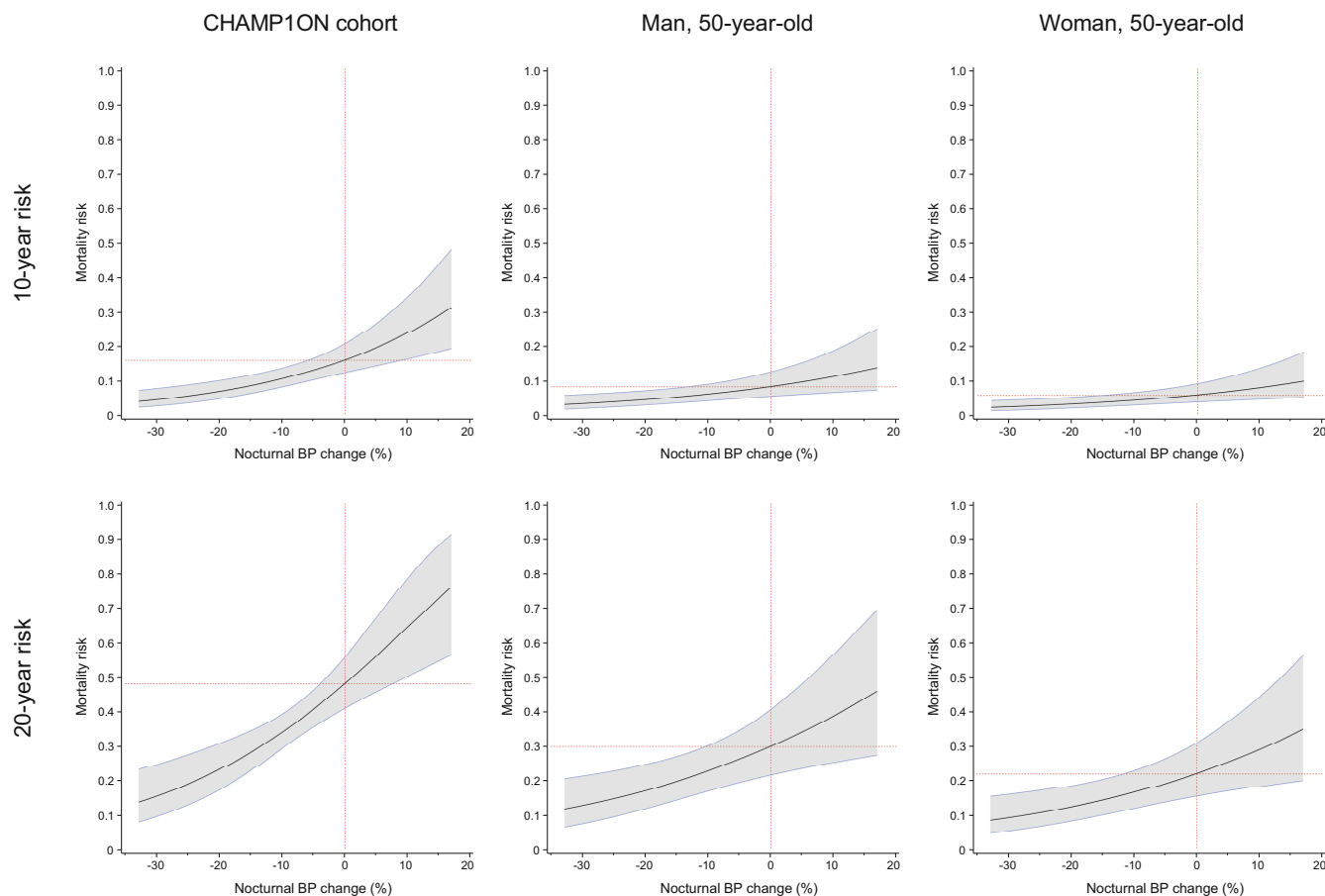
Consistent with the higher prevalence and severity of hypertension, echocardiographic measures documented a higher prevalence of concentric left ventricular remodelling and increased relative wall thickness in reverse dippers (Table 1). The prevalence of CKD stages III to IV increased across dipping groups, being the lowest in dippers and the highest among reverse dippers (9% vs. 14% vs. 22%;  $P = 0.039$ ). Furthermore, compared with dippers, nondippers and reverse dippers showed increasingly high postural dip in SBP during the orthostatic hypotension test, in agreement with a greater prevalence of CAN (13% vs. 21% vs. 41%;  $P = 0.003$  [Table 1]).

#### 3.3 | Survival analysis by BP dipping patterns

After 6251 person-years of follow-up (median [range] follow-up 21.0 [1.1–22.0] years), a total of 136 deaths (39%) occurred (21.8 deaths per 1000 person-years). Kaplan-Meier and model-predicted survival curves for each dipping group are shown in Figure 2. The survival probability decreased progressively across groups, with a mean overall survival of  $18.6 \pm 4.6$  years for dippers,  $17.5 \pm 5.3$  years for nondippers, and  $16.1 \pm 5.3$  years for reverse dippers (log-rank test  $P < 0.001$ ). Reverse dippers showed an increased risk for all-cause mortality compared with the other dipping categories in the unadjusted Cox regression analysis (HR 2.5 [95% CI 1.5–4.0] vs. dippers and 1.7 [95% CI 1.1–2.7] vs. non-dippers [Figure 3A]). In Model 1, adjusted for traditional



**FIGURE 3** Hazard ratios (HRs) and 95% confidence intervals for 21-year all-cause mortality for reverse dipping (A) and for each 1% increase in nocturnal blood pressure (BP) dipping (B). All multivariable models were adjusted for age, sex, body mass index, glycaemic control, estimated glomerular filtration rate, and type and duration of diabetes. Additionally, models were adjusted for office systolic BP (SBP; Model 1), 24-hour BP control (Model 2), isolated nocturnal hypertension (Model 3) or office SBP and number of antihypertensive medications (Model 4)



**FIGURE 4** Relationship between percentage nocturnal blood pressure (BP) change and all-cause mortality risk. The relationship between nocturnal BP change and all-cause mortality risk at 10 years and 20 years of follow-up is reported in the whole study cohort and in two representative patients (50-year-old man and woman)

cardiovascular risk factors (namely, age, sex, BMI, glycaemic control, eGFR, type and duration of diabetes and office SBP), reverse dipping was associated with a 2.2-fold increase in the risk of all-cause mortality

compared with dipping (HR 2.2 [95% CI 1.3-3.8]) and with a 1.8-fold risk increase compared with nondipping (HR 1.8 [95% CI 1.1-2.9]). The mortality risk associated with reverse dipping remained consistently



higher than that of other dipping patterns after further adjustments for 24-hour BP control (Model 2), isolated nocturnal hypertension (Model 3), and number of medications (Model 4), as shown in Figure 3A. There was no significant difference in mortality risk between nondippers and dippers (Model 1: HR 1.3 [95% CI 0.9-1.9]) unless reverse dippers were grouped together with nondippers (Model 1: HR 1.5 [95% CI 1.1-2.1]). Furthermore, there was no interaction of type of diabetes or age with dipping status in predicting mortality in all models.

### 3.4 | Survival analysis by nocturnal percent dipping

To further explore the predictive role of nocturnal BP dipping, considered as a continuous variable, we also tested the reduction in mortality risk associated with a 1% increase in nocturnal BP dipping (Figure 3B). Dipping showed a significant prognostic value in the unadjusted model (HR 0.96 [95% CI 0.94-0.98]) as well as in the adjusted Models 1 to 4 (Figure 3B), averaging a 3% to 4% reduction in mortality risk for each 1% increase in nocturnal BP dipping. There was no interaction of type of diabetes or age with percent dipping in predicting mortality in all models.

We used prediction profilers to examine the shape of the relationship between nocturnal BP change and all-cause mortality risk at 10 or 20 years of follow-up. In the whole study cohort and in two paradigmatic cases (ie, a 50-year-old man and woman), dose-response curves showed positive and quasi-linear correlations (Figure 4).

## 4 | DISCUSSION

This retrospective longitudinal study demonstrates the prognostic value of BP circadian variations in a large cohort of middle-aged patients with longstanding diabetes followed up for more than 20 years. At enrolment, approximately 50% of participants had non-dipping or reverse-dipping BP patterns at the 24-hour ABPM, which were associated with more intensively treated but often uncontrolled hypertension ("masked" in almost 20% of cases), concentric left ventricular remodelling, DKD and CAN. We found that a reverse-dipping pattern substantially reduced survival probability compared with both dipping and nondipping patterns, despite otherwise similar group characteristics and after accounting for traditional cardiovascular risk factors and plausible mediators, including office, 24-hour, and isolated nocturnal hypertension. Consistently, we found that average night-time versus daytime SBP ratio positively correlated with mortality risk in a quasi-linear fashion. These findings corroborate the current recommendations<sup>28,34</sup> to implement 24-hour ABPM as a risk stratification tool to identify abnormal BP patterns in high- and very-high-risk populations, such as patients with longstanding diabetes.

Altogether, our study findings suggest that reverse dipping is a more extreme phenotype of nondipping, characterized by higher severity of autonomic dysfunction, increased risk of subclinical organ damage, and, above all, reduced survival probability. Reverse dippers showed higher 24-hour BP values than other groups, and, consistently,

had a higher prevalence of concentric left ventricular remodelling, as previously reported.<sup>25</sup> Along with sustained hypertension, the nondipping pattern has been associated with microvascular complications in diabetes, particularly CAN and nephropathy.<sup>14,17,18,35</sup> CAN is characterized by sympathovagal imbalance, a pathological condition also found in abnormal circadian BP patterns.<sup>35,36</sup> Indeed, CAN was increasingly prevalent across groups and was three times more frequent in reverse dippers than dippers, thereby confirming the close association between these two conditions. Both nondippers and reverse dippers showed a greater BP dip during the orthostatic hypotension test, which is also an established feature of autonomic neuropathy.<sup>14,18,37,38</sup> In addition, reverse dippers were characterized by a higher prevalence of nephropathy, especially with a reduced eGFR, in accordance with previous reports.<sup>10,17,35</sup>

We described a quasi-linear association between mortality risk modification and night-to-day SBP ratio, as previously reported in a shorter-term study,<sup>22</sup> and an increased risk of death in the broad category of subjects with impaired (<10%) nocturnal BP dipping, including both nondippers and reverse dippers, compared with dippers. The latter finding, however, was largely driven by the reduced survival probability of reverse dippers. In fact, after accounting for plausible confounders, we found that nondippers do not have an increased risk of all-cause mortality compared with dippers, while the mortality risk is increased by approximately twofold in reverse dippers compared with both dippers and nondippers. This observation is consistent with the study by Eguchi et al,<sup>19</sup> showing an increased 6-year cardiovascular risk for reverse dippers, but not for nondippers, in patients without diabetes, and suggests that previous evidence on the increased risk of nondippers may have been influenced by the unaccounted presence of reverse dippers. Indeed, the important peculiar characteristics of reverse dippers in terms of clinical features and prognosis, pointed out here, have been often overlooked, this group being most frequently combined with nondippers and characterized in patients without diabetes.<sup>21,38,39</sup>

A major strength of our study is the unusually long follow-up duration, extending over 20 years, that has allowed, for the first time, a long-term assessment of the time-dependent prognostic role of reverse dipping in diabetes. According to our data, in fact, the negative effects of reverse dipping are only marginally relevant during the first 5 years of observation (or for even longer without accounting for traditional risk factors), becoming increasingly evident afterwards (Figure 2). This novel information provides new insight into the importance of reverse dipping as an independent prognostic factor for all-cause mortality in diabetes, which was previously supported by a limited number of studies with follow-up periods shorter than 10 years.<sup>19,21-23</sup>

The increased mortality risk related to reverse dipping does not seem specific to diabetes, given that a similar increase in the risk for cardiovascular events<sup>39</sup> and all-cause mortality<sup>40</sup> has been previously reported in the general population. However, the impact of reverse dipping may be greater in patients with diabetes, for its prevalence in this group has been reported to be three to five times greater compared with the general population,<sup>39,40</sup> underscoring the particular need for diabetic patients to be screened for dipping abnormalities.



Our data do not support the prognostic role of extreme dipping (>20%) for mortality and CVD, which is currently debated,<sup>41</sup> as we did not find a J-shaped association between dipping and mortality risk. Extreme dippers, however, were scarcely represented in our cohort (6%) and therefore this finding should be confirmed in larger studies.

Treatment-wise, there are currently no effective drugs specifically targeting dysautonomia, which may be involved in the pathogenesis of abnormal circadian BP patterns. Nevertheless, two drugs have shown potential for CAN reversal, namely, pioglitazone<sup>42</sup> and sodium-glucose cotransporter-2 inhibitors,<sup>43</sup> thereby representing a promising pharmacological option against BP circadian alterations. Given the lack of specific treatments targeting autonomic imbalance, the most used strategy to address nondipping is to modulate the dosage and timing of antihypertensive medications, preferring nighttime administration of BP-lowering drugs.<sup>44</sup> The association between reduced nocturnal dipping and dysautonomia alone could contribute to the increased mortality risk observed with reduced dipping in frail patients (eg, increased risk of falls); in addition, reverse dippers are characterized by high rates of masked and uncontrolled hypertension, which can increase mortality if untreated. However, despite the recommendations of international guidelines, not all patients undergo ABPM in clinical practice, and some may never be diagnosed with abnormal dipping patterns. We therefore support the role of ABPM as an inexpensive, widely available screening and monitoring tool for the diagnosis of abnormal BP circadian variations, pursuing an optimized treatment and management of patients with diabetes and dysautonomia.

There are some limitations to our study. First, in the CHAMP1ON study cohort, BP patterns were assessed only at the enrolment visit without collecting information on the individual sleeping pattern; nevertheless, previous studies have found a high reproducibility of ABPM-based classification of dipping patterns in diabetics<sup>45</sup> and patients working nightshifts were excluded. Second, while multivariable models were implemented to account for major potential confounders, models were not adjusted for all available variables (eg, medications, microvascular complications) to avoid model overfitting due to the relatively small size of the reverse-dippers group. Third, the CHAMP1ON study cohort did not undergo characterization of previous CVD or comorbidities besides diabetes-related complications, thus hindering the possibility of conducting subgroup analyses for different cardiovascular risk categories. Fourth, the CHAMP1ON cohort is constituted by a predominantly White population from a single centre; this could limit the generalization of our results to other ethnicities. Fifth, we could not retrieve data on clinical and biochemical variables nor treatment changes during the follow-up period. Finally, patients were recruited between 1999 and 2000, a time when best medical practice could not benefit from the currently available antidiabetic drugs, and when glucose- and lipid-lowering goals were not as strict as today. This is reflected by the loose glycaemic and metabolic control observed in our cohort, which may have contributed to the high death rate and prevalence of microvascular complications. In fact, a similar overall death rate has been reported in a large cohort of patients with diabetes followed up for 20 years.<sup>46</sup>

In conclusion, our study demonstrates the critical prognostic role of abnormal dipping patterns in patients with diabetes, irrespective of BP control and other risk factors, providing long-term data for all-cause mortality supported by the longest observation period reported in the literature to date. These findings support the screening for abnormal BP patterns as a risk stratification tool in patients with diabetes.

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## CONFLICT OF INTEREST

The authors have no conflicts of interest pertinent to this study.

## PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14798>.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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