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Functional Regression Methods for Estimating 24-Hour Ambulatory Blood Pressure and Heart Rate Parameters in Narcolepsy Type 1

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Keywords
Ambulatory blood pressure monitoring · Nocturnal blood pressure dip · Diurnal pattern · Narcolepsy type 1

Abstract
Introduction: The nocturnal dip, a physiological drop in nocturnal blood pressure (BP), is driven by the autonomic nervous system. A reduction of <10% during nocturnal sleep versus daytime wakefulness is considered a "non-dipping" BP pattern and associated with increased cardiovascular disease risk in the general population. This study aimed to compare different methods for estimating BP and heart rate (HR) nocturnal dip from ambulatory BP monitoring (ABPM) data in individuals with narcolepsy type 1 (NT1). ***Methods:*** Baseline ABPM data were from participants with NT1 in the randomized TAK-994 phase 2 clinical trial (NCT04096560). Sleep period time (SPT) windows were estimated from raw accelerometer data overlapping with baseline and week 3 ABPM visits. Three approaches estimated BP and HR dip: (1) fixed-window, with daytime defined as 06:00 to 22:00, nighttime as 00:00 to 06:00, and dip defined as a drop from the daytime to nighttime window average; (2) 24-h pattern employing a two-component cosinor model to estimate a continuous 24-h pattern of BP and HR, and defining dip as a drop from pattern average to its lowest point; and (3) actigraphy-based, with dip defined as a drop from non-SPT to SPT average of BP and HR, utilizing algorithmically identified SPT aiming to best reflect participants' actual sleep periods. ***Results:*** The analytic sample consisted of 31 participants with NT1. Comparing actigraphy-based dip with fixed-window and 24-h pattern dips, the 24-h pattern dip had higher Pearson's correlation than the fixed-window dip across all three parameters (0.91 vs. 0.87, 0.88 vs. 0.68, and 0.88 vs. 0.56 for systolic BP [SBP], diastolic BP [DBP], and HR, respectively). We found substantial between- and within-participant variability in SPT timing and duration. A total of 61% of participants had a fixed-window SBP dip <10%, and 41% had a fixed-window DBP dip <10%. The 30th percentile of SBP/DBP dip varied substantially across calculation methods: 3.8%/8.6% (fixed-window), 6.8%/14.1% (24-h pattern), and 6.7%/12.1% (actigraphy-based). ***Conclusion:*** Estimated dip values from the 24-h pattern approach with a two-component cosinor model for BP and HR were strongly correlated with actigraphy-based dip values, which utilized an objective algorithm to identify participants' sleep. The 24-h pattern approach offers a robust alternative to the fixed-window method for assessing dipping, especially in populations with sleep

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timing variations and disturbances, like NT1, and does not require simultaneous actigraphy measurement. The classification of a "non-dipper" varies depending on both the dip type (SBP vs. DBP) and the dip estimation method.

Introduction

In healthy populations, blood pressure (BP) nocturnal dip is an autonomic nervous system-driven physiological phenomenon, where nocturnal BP drops by 10–20% versus daytime BP (although this range is considered arbitrary [1]). A "non-dipping" BP pattern, defined as reduction of <10%, is associated with increased cardiovascular disease risk for systolic BP (SBP) [2] and mortality for SBP or diastolic BP (DBP) [3] in the general population. Additionally, lower SBP dip values were associated with higher risk of total, cardiovascular, and non-cardiovascular mortality [4].

Large-scale clinical trials involving ambulatory BP monitoring (ABPM) define the sleep timeframe for nocturnal BP calculation using various methods, including self-reported daily sleep diaries [2, 3], individually predetermined sleep schedules [5], and fixed daytime and nighttime windows [4, 6]. Self-reporting problems include recall, compliance, and the subjectivity of self-reporting [7]. Predetermined sleep schedules dismiss night-to-night sleep variations and schedule deviations. Similarly, with a fixed-window approach, an individual's true sleep time may differ from the predefined window and vary daily. Functional regression methods, specifically cosinor models [8], are widely employed for estimating circadian rhythms in chronobiology, offering a data-driven, objective approach for characterizing 24-h BP patterns from ABPM data [9–11] and other 24-h physiological time-series, like activity from actigraphy [12].

Narcolepsy type 1 (NT1), a rare neurologic disease caused by loss of orexin neurons, is characterized by excessive daytime sleepiness, cataplexy, hallucinations, sleep paralysis, and disrupted nighttime sleep (DNS) with multiple arousals and sleep instability [13–15]. Untreated individuals with NT1 have increased autonomic symptoms versus controls [16]. Previous studies report that 30.6% of drug-free participants with NT1 were DBP non-dippers versus 3% of controls [5]. Participants with NT1 also had higher sleeping heart rate (HR) than matched controls [6, 17]. Furthermore, they are at risk for cardiovascular diseases, though the contributing factors are unclear and likely multifactorial [18–21]. TAK-994, an oral orexin receptor 2-selective agonist, aimed to mimic the orexin neuropeptide role in promoting wakefulness and reducing NT1 symptoms [22]. TAK-994 was investigated in a phase 2 randomized trial in participants with narcolepsy (NCT04096560) and stopped prematurely due to liver safety signals [23]; aligning with US Food and Drug Administration guidance [24], it included baseline and during-treatment ABPM.

Despite the clinical importance of nocturnal BP and HR dipping, there is limited evidence on how different estimation methods perform in populations with highly irregular sleep patterns such as NT1. This gap is important because misestimation of nocturnal dipping can lead to inaccurate cardiovascular risk evaluation and misinterpretation of treatment effects. To our knowledge, no prior study has systematically compared fixed-window, 24-h pattern modeling, and actigraphy-based approaches for dip estimation in NT1. This study evaluates different methods for estimating BP and HR nocturnal dip from ABPM data and estimates ambulatory SBP, DBP, and HR parameters using single-visit baseline ABPM data in participants with NT1.

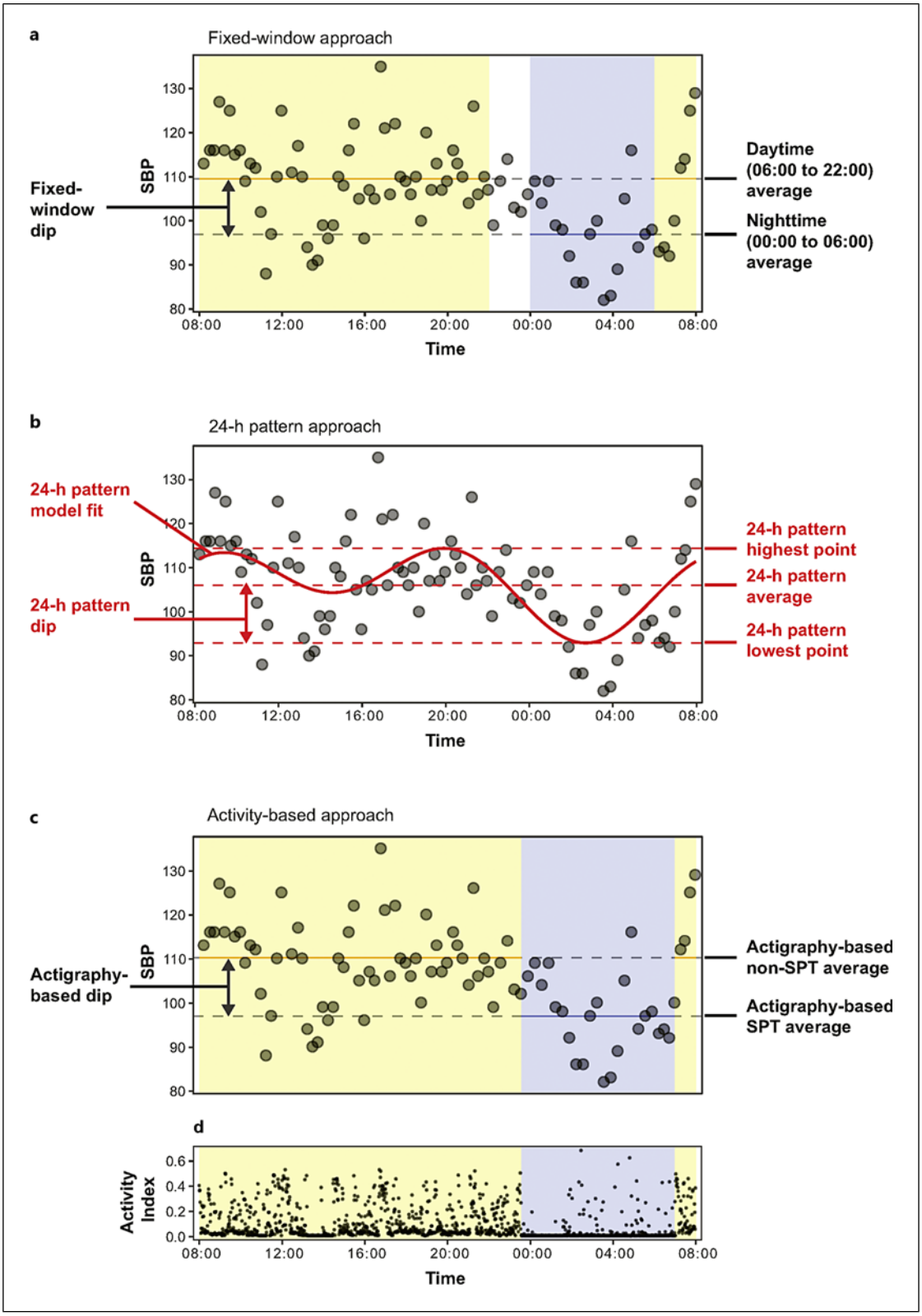
Methods

Study Design and Population

Data were from the phase 2, part B, randomized, placebo-controlled global trial evaluating TAK-994's efficacy and safety in participants with NT1 (NCT04096560) aged 18–65 years, diagnosed using International Classification of Sleep Disorders-Third Edition criteria [25] and confirmed through polysomnography and multiple sleep latency tests. Inclusion criteria included baseline SBP <140 mm Hg and DBP <90 mm Hg (median across three measurements following rest for >10 min); participants could have history of hypertension and take antihypertensive medication treatment provided their BP met these criteria. Participants discontinued all narcolepsy medications, if applicable, were randomly assigned to placebo or one of three TAK-994 doses for 8 weeks, and continuously wore actigraphy devices. Further inclusion criteria, study design, and trial results are reported by Dauvilliers et al. [23]. The CONSORT reporting checklist is in online supplementary materials (for all online suppl. material, see https://doi.org/10.1159/000550314).

Digital Technology

The Spacelabs 90207 ABPM device (Spacelabs Healthcare, Snoqualmie, WA) was used for 24-h ABPM at baseline and weeks 2, 3, and 6. Four



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observations per hour were recorded from 06:00 to 22:00 and then three from 22:00 to 06:00, including SBP (mm Hg), DBP (mm Hg), and HR (beats per minute). Rare missing observations were identified and flagged by the proprietary algorithm. Failed ABPM measurements were typically due to movement artifacts, improper cuff placement, or equipment malfunctions and were retried in a few minutes, typically resulting in successful measurements. Analyzed data were limited to 24 h of recording in case data exceeded the 24-h window. This work only uses baseline visit ABPM data.

Empatica's EmbracePlus wearable device (Empatica, Boston, MA, USA) continuously measured wrist motor movement, recorded as 3-axis accelerometer data at a sampling frequency of 64 Hz, from baseline through week 8. For visualization purposes, subsecond-level data were aggregated at minute-level using Activity Index, an open-source summary measure of physical activity intensity [26, 27]. Participant device non-wear was identified at the minute-level with Empatica's proprietary algorithm. This work uses accelerometer data collected during periods overlapping with the 24-h ABPM recordings at baseline and week 3.

Ambulatory BP and HR Parameters

These were derived from baseline visit ABPM data per participant and per parameter (SBP, DBP, HR) using three distinct approaches: fixed-window, 24-h pattern, and actigraphy-based. Figure 1 shows these approaches for calculating BP and HR dip parameters using one participant's baseline SBP and actigraphy data.

Fixed-Window Approach

Daytime was defined as 06:00 to 22:00 and nighttime as 00:00 to 06:00; they excluded the "retiring" period (22:01 to 23:59) to minimize influence of age- and lifestyle-related differences in sleep times [28]. Next, ABPM data were averaged within the fixed-window timeframes. Finally, the "fixed-window dip" was calculated as 100% × (daytime average−nighttime average)/(daytime average).

24-Hour Pattern Approach

A cosinor model with two periodic components of 24 h and 12 h was employed to estimate a continuous 24-h pattern best fitting the collected ABPM data, described as follows:

$$Y(t) = M + A_1\cos\left(\frac{2\pi t}{24} - \phi_1\right) + A_2\cos\left(\frac{4\pi t}{24} - \phi_2\right) + e(t)$$

where t represents the time of an ABPM measurement (0–24 h), M is the average value, A_1 and A_2 are the amplitudes of the first and second harmonic components (cosine functions), ϕ_1 and ϕ_2 are the phases of the first and second harmonic components, $Y(t)$ is the observed data, and $e(t)$ is the error. We selected a two-component cosinor model based on Fernández et al. [11], who found it suitable for capturing BP circadian patterns, including sleep-related nocturnal dip and up to two daytime peaks. The model-fitted 24-h pattern was then used to derive the 24-h pattern average, lowest and highest points, and "24-h pattern dip," calculated as 100% × (24-h pattern average−24-h pattern lowest point)/(24-h pattern average). We proposed a dip definition of drop from average to lowest point (rather than drop from highest to lowest points, i.e., pattern amplitude) to emphasize capturing below-average BP and HR fluctuations typically expected during nighttime, as opposed to above-average fluctuations characteristic of daytime periods. The pattern amplitude dip was also explored.

Actigraphy-Based Approach

Accelerometer data were employed to identify the sleep period time (SPT) window, defined as the interval between sleep onset and final awakening during the primary nighttime sleep episode. SPT estimates were derived using van Hees et al. [29] algorithm from raw accelerometer data. Because actigraphy-based estimation of SPT windows can be challenging in populations with fragmented or atypical sleep-wake patterns, including NT1, all automatically identified SPT windows were subsequently reviewed alongside the underlying raw accelerometer data and manually corrected when necessary by a researcher who was blinded to the ABPM data. Next, ABPM data were averaged within the SPT window and remaining non-SPT time periods overlapping with the ABPM recording

Fig. 1. Three approaches for calculating BP and HR parameters. Each displays the same exemplary SBP data collected from a single participant during the baseline visit. **a** In the fixed-window approach, the shaded areas denote the daytime (06:00 to 22:00, shaded yellow) and nighttime (00:00 to 06:00, shaded blue) windows; SBP dip equals 11.6% (100% × [109.6−96.9]/109.6). **b** In the 24-h pattern approach, the red continuous line represents the model-estimated 24-h pattern; SBP dip equals 12.0% (100% × [110.2−96.9]/110.2). **c** In the actigraphy-based approach, the shaded areas denote the identified SPT and non-SPT time periods data; SBP dip equals 11.1% (100% × [110.0−97.8]/110.0). **d** The underlying minute-level actigraphy data illustrate reduced activity during the SPT window.

window. Finally, the "actigraphy-based dip" was calculated as 100% × (non-SPT average–SPT average)/(non-SPT average). While this method aims to best reflect participants' primary nighttime sleep window, the identified SPT windows do not represent ground-truth sleep periods.

Statistical Analysis

The analytic sample included participants across all randomization arms who completed the baseline ABPM visit and had actigraphy data coverage of ≥90% during that visit. This coverage threshold has been previously used in large epidemiological studies with continuous wrist-worn wearable device protocols to determine whether a given day is included in downstream analyses [30, 31].

We first aggregated (mean [SD]) values for baseline ambulatory SBP, DBP, and HR parameters. Because the three dip measures quantify BP and HR variability using different methodological definitions, their values for given participants are not expected to be directly comparable; however, we aimed to assess the strength and direction of their associations. We estimated Pearson correlation coefficients (r) between the three dip values across three methods for baseline SBP, DBP, and HR. Sample percentiles (0th, 5th, 10th, . . ., 95th, 100th) were calculated for each dip measure. In a sensitivity analysis, we compared the correlation between actigraphy-based dip and 24-h pattern-based dip, where the latter was defined as drop from the pattern's highest to lowest point (i.e., amplitude dip), rather than our definition of drop from 24-h pattern average to lowest point.

Next, we calculated each participant's average SPT window timing and duration from the time window overlapping with baseline ABPM visit, and change from baseline to week 3 ABPM visit. Aggregated values (mean [SD]) were reported across the analytic sample. We also calculated each participant's proportion of the SPT window overlapping with the fixed 00:00 to 06:00 nighttime frame, and conversely, proportion of the 00:00 to 06:00 window overlapping with the SPT, at baseline and week 3, reporting aggregated values. Lastly, we visualized minute-level activity intensity patterns, SPT windows, and the fixed nighttime frame at baseline and week 3 ABPM visits. All preprocessing and statistical analyses were performed using *R* software (version 4.3.0).

Results

Participants

Baseline ABPM data were collected from 67 participants; 31 (46.3%) had completed the baseline ABPM visit with ≥90% actigraphy data coverage during that visit and were included in the analytic sample (Table 1). The baseline mean age was 28.6 years, 54.8% were female, and 74.2% were White; mean values for average sleep latency on the Maintenance of Wakefulness Test, Epworth Sleepiness Scale score, and weekly cataplexy rate were aligned with expected profiles of untreated (or narcolepsy medication-discontinued) participants with NT1 observed in the whole sample [23].

Table 1. Baseline participant demographics and clinical characteristics

Characteristic	Analytic sample
Participants, *n*	31
Age, years	
Mean (SD)	28.6 (10.3)
Median (min, max)	24 (18, 55)
Sex, *n* (%)	
Female	17 (54.8)
Male	14 (45.2)
Ethnicity, *n* (%)	
Not Hispanic or Latino	30 (96.8)
Hispanic or Latino	0 (0)
Unknown or not reported	1 (3.2)
Race, *n* (%)	
White	23 (74.2)
Asian	5 (16.1)
Black	1 (3.2)
Multiple or not reported	2 (6.5)
Average sleep latency on Maintenance of Wakefulness Test, min	
Mean (SD)	6.2 (6.0)
Median (min, max)	4 (0, 21)
Epworth Sleepiness Scale score[a]	
Mean (SD)	16.7 (3.5)
Median (min, max)	17 (8, 22)
Weekly cataplexy rate, episodes, *n*	
Mean (SD)	13.6 (14.0)
Median (min, max)	9 (0, 72)
History of hypertension, *n* (%)	1 (3.2)
Hypertension medication, *n* (%)	1 (3.2)

max, maximum; min, minimum. [a]Range: 0–24, scores from 11 to 24 suggest excessive daytime sleepiness.

Baseline Ambulatory BP and HR Parameters

Baseline mean (SD) SBP, DBP, and HR fixed-window dips were 7.5% (5.9), 12.0% (8.2), and 16.6% (6.8), respectively (Table 2); 24-h pattern dips were 10.2% (4.3), 16.1% (6.4), and 19.2% (6.3), respectively; and actigraphy-based dips were 9.4% (5.5), 15.1% (6.9), and

Table 2. Baseline ambulatory BP and HR parameters

Parameter, mean (SD)	SBP, mm Hg	DBP, mm Hg	HR, bpm
Fixed-window approach[a]			
Daytime average	113.6 (7.7)	70.2 (5.4)	76.0 (7.5)
Nighttime average	105.0 (10.1)	61.6 (6.1)	63.5 (8.3)
Dip, %	7.5 (5.9)	12.0 (8.2)	16.6 (6.8)
24-h pattern approach			
Average	111.3 (8.0)	67.8 (5.1)	72.7 (7.5)
Highest	120.5 (8.0)	76.8 (5.6)	84.4 (8.0)
Lowest	100.1 (9.2)	57.0 (6.7)	58.9 (8.9)
Dip, %	10.2 (4.3)	16.1 (6.4)	19.2 (6.3)
Actigraphy-based approach			
Daytime average	115.1 (8.0)	71.5 (5.4)	78.2 (7.6)
Nighttime average	104.2 (8.9)	60.6 (6.1)	63.3 (8.1)
Dip, %	9.4 (5.5)	15.1 (6.9)	19.0 (5.8)

BP, blood pressure; bpm, beats per minute; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure. [a]Fixed-window daytime was 06:00 to 22:00, and nighttime was 00:00 to 06:00.

19.0% (5.8), respectively. DBP dips had higher means (SDs) than SBP dips across the three methods. Online supplementary Figures S1–S3 show the raw BP and HR data and corresponding continuous 24-h patterns derived from the baseline ABPM visit data per participant in the analytic sample, illustrating the flexibility of the two-cosinor statistical model in fitting ABPM data to estimate BP and HR 24-h patterns. We also calculated the timing of the lowest and second-lowest minimum points (i.e., local minima) in the 24-h SBP, DBP, and HR patterns from the baseline ABPM visit, and distribution of Activity Index in the ±5 min vicinity of those (online suppl. Fig. S4).

Comparing fixed-window and 24-h pattern dip values, SBP showed very high correlation ($r = 0.82$), and DBP and HR showed high correlations ($r = 0.68$ and $r = 0.61$, respectively; Fig. 2). When comparing actigraphy-based dip with, respectively, fixed-window dip and 24-h pattern dip, the latter had higher correlation than the former across all three parameters (SBP, $r = 0.91$ vs. $r = 0.87$; DBP, $r = 0.88$ vs. $r = 0.68$; HR, $r = 0.88$ vs. $r = 0.56$; Fig. 2). Through additional analyses, actigraphy-based dip had slightly higher correlation with 24-h pattern dip using dip definition of drop from pattern average to lowest point versus drop from pattern highest to lowest point (SBP, $r = 0.91$ vs. $r = 0.88$; DBP, $r = 0.88$ vs. $r = 0.84$; HR, $r = 0.88$ vs. $r = 0.87$; online suppl. Fig. S5).

Online supplementary Table S1 displays percentiles of BP and HR dip values across the three methods. In relation to the widely cited 10% dip threshold for defining non-dippers, 61% of participants had SBP fixed-window dip <10%. In contrast, 41% had DBP fixed-window dip <10% (they all also had SBP fixed-window dip <10%). This suggests substantial differences in "BP non-dipper" classification using the fixed-window approach based on whether the 10% dip threshold is applied to SBP or DBP. Alternatively, the 30th percentiles of the dip (i.e., dip value below which 30% of the dip values in the sample fall; close to previously reported 30.6% of DBP non-dippers in untreated NT1 [5]) for the fixed-window, 24-h pattern, and actigraphy-based methods were 4.2%, 6.8%, and 6.9% for SBP, 8.6%, 14.1%, and 12.1% for DBP, and 14.2%, 16.0%, and 17.6% for HR dip, respectively. These results suggest that the dip thresholds separating the lowest third of the sample vary substantially depending on dip derivation method.

Actigraphy-Based SPT

Algorithmically identified actigraphy-based SPT windows were available for all 31 participants for baseline ABPM visit and for 26 (83.9%) for the week 3 ABPM visit. Figure 3 illustrates actigraphy-based activity levels and SPT windows for the two ABPM visits, showing between- and within-participant variability.

The baseline median (interquartile range [IQR]) sleep window start clock time was 23:06 (22:32 to 00:31), and range was 18:00 to 08:07. Among participants with a SPT detected at baseline and week 3, the median (IQR) difference in SPT window start time between the two visits was 42 (26–73) min and range was 4–274 min. Additional summary statistics are provided in online supplementary Results. These results indicate substantial between- and

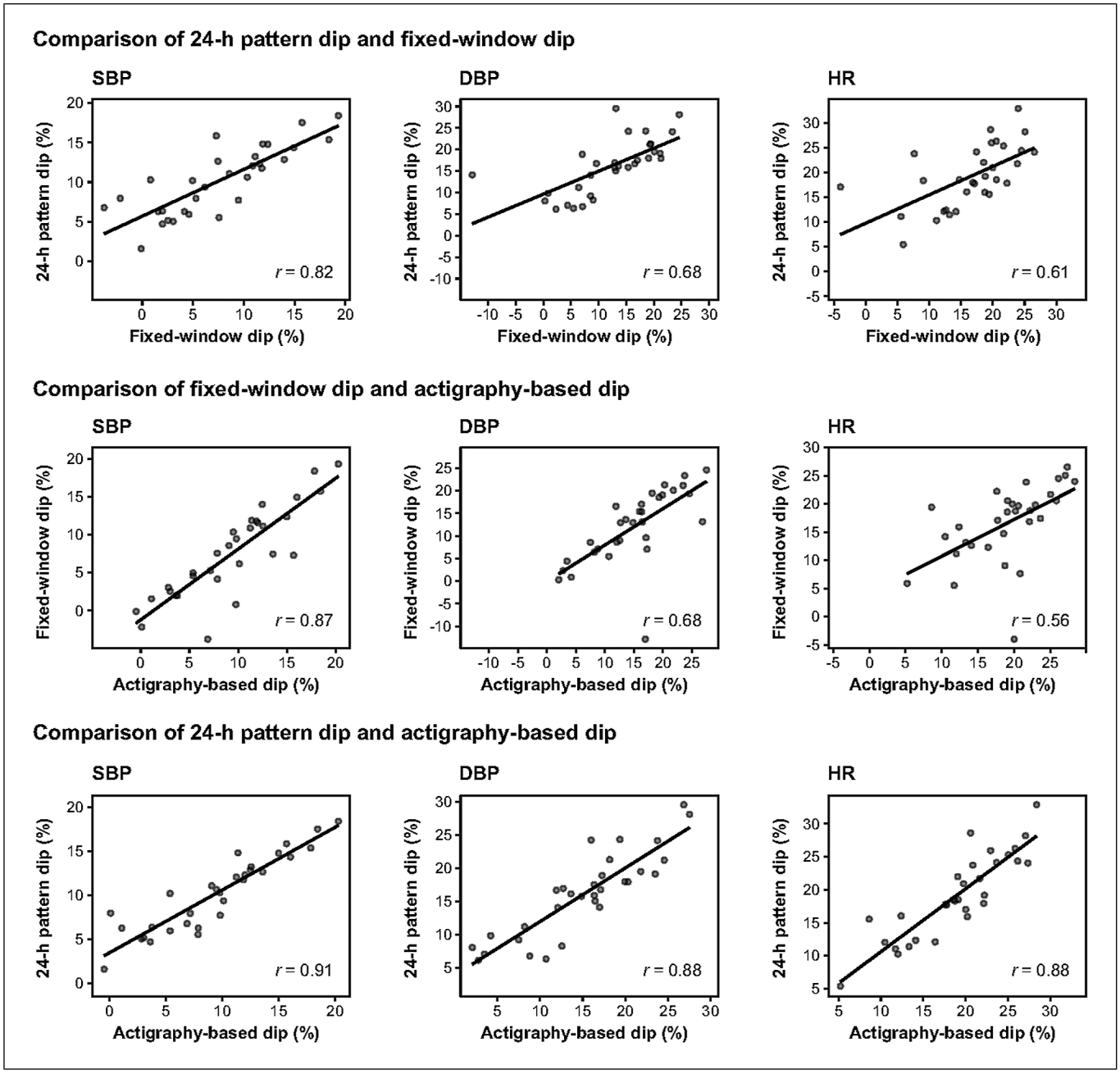

Fig. 2. Comparison of dip values between the fixed-window, 24-h pattern, and actigraphy-based approaches. Points represent individual dip values. The black lines and correlation values correspond to a linear fit between the values. The actigraphy-based dip had higher correlation with the 24-h pattern dip than with the fixed-window dip across all three parameters ($r = 0.91$ vs. $r = 0.83$, $r = 0.89$ vs. $r = 0.67$, and $r = 0.85$ vs. $r = 0.58$ for SBP, DBP, and HR, respectively).

within-participant variability in duration and timing of the sleep window across the two ABPM visits. We also observed that although the fixed nighttime window was typically covered by the SPT window, only about two-thirds of the SPT window (often extending beyond 6 h) typically occurred within this fixed-window.

A notable case is where actigraphy data indicated that a participant's sleep occurred in the later morning, with

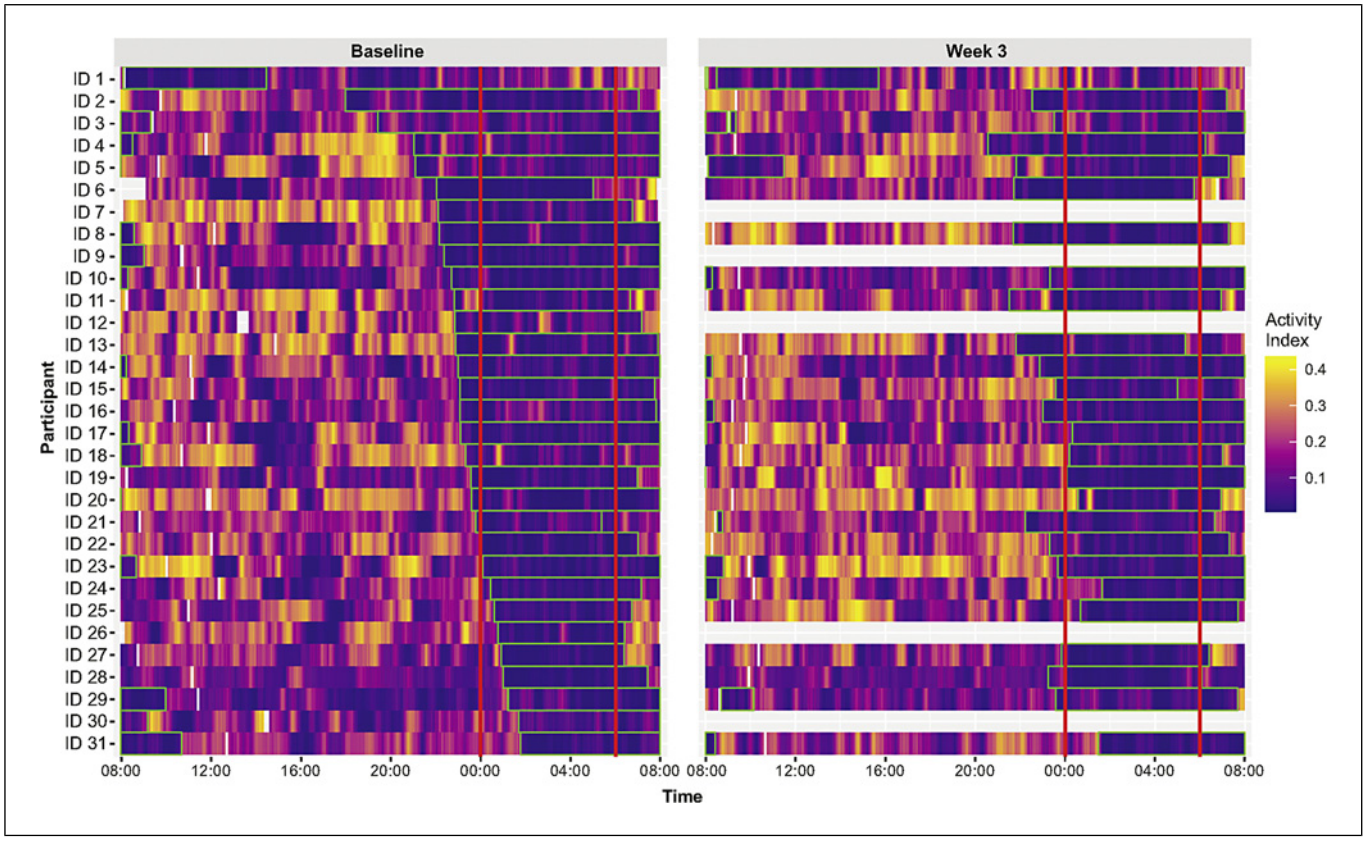

Fig. 3. Actigraphy-based SPT windows during 24-h ABPM measurement visits, illustrating both between- and within-participant variations. Each row represents a single participant's data at baseline (left panel) and week 3 (right panel) and is ordered based on their sleep window timing during the baseline ABPM visit. Tile colors indicate minute-level Activity Index values, with lighter colors representing greater motor activity; Activity Index values were winsorized at 0.44 (90th percentile of the sample) for visualization. Uncolored tiles indicate minutes when the device was not worn. Algorithmically identified SPT windows are outlined in green; red vertical lines denote the fixed nighttime window from 00:00 to 06:00. Data indicate substantial between- and within-participant variability in both duration and timing of the SPT window across the two ABPM visits.

0% overlap with the 00:00 to 06:00 window. Accordingly, their SBP, DBP, and HR physiological decrease during the estimated sleep period fell into the daytime fixed-window (06:00 to 22:00), leading to negative dip values as calculated through the fixed-window approach (SBP, −12.9%; DBP, −4.0%; HR, −3.8%; participant ID 1, online suppl. Fig. S1–S3). In contrast, positive dip values were observed for the 24-h pattern (14.1%, 17.0%, and 6.8%) and actigraphy-based (17.0%, 20.0%, and 6.9%) approaches for SBP, DBP, and HR dip, respectively.

Discussion

Utilizing ABPM data from clinical trial participants with NT1, this study investigated three approaches for estimating BP and HR dipping: fixed-window, 24-h pattern, and actigraphy-based. The simple-to-implement fixed-window approach assumes that participants' true sleep periods consistently align with predefined time windows; however, this may not hold true for individuals with DNS (like in NT1 [32]) with irregular sleep-wake cycles [33], or with idiopathic hypersomnia and long sleep times [34].

In contrast, the data-driven 24-h pattern approach does not rely on fixed-windows or self-reported sleep times to define the nocturnal sleep window. The approach employs a two-component cosinor model, aiming to balance flexibility in modeling gradual BP and HR fluctuations with reduced risk of overfitting or undue influence from outliers that may arise with more complex models. This model handles uneven ABPM sampling frequencies and can be implemented in standard statistical software with negligible computational cost. If

applied at scale, goodness-of-fit metrics could be easily computed to flag cases with poor model fit or unusual data patterns, enabling automated quality control. The 24-h pattern dip was calculated based on the drop from 24-h pattern average to lowest point, capturing below-average BP and HR fluctuations typically expected during nighttime [35]. In supplementary analyses, we found that this dip definition correlated higher with the actigraphy-based dip than calculations based on the drop from 24-h pattern highest to lowest points.

The actigraphy-based approach objectively identifies the SPT window based on extended intervals of inactivity and therefore enables BP and HR dip calculation based on individualized estimates of sleep-wake periods. However, this approach carries an important practical limitation: it depends on consistent participant adherence to wearing a wrist-worn accelerometer throughout the ABPM monitoring period. In our study, only 31 of 67 participants (46.3%) achieved the predefined 90% coverage threshold at the baseline ABPM visit. As a result, the analytic sample was substantially smaller than the full study cohort. This level of missingness underscores the trade-off between using actigraphy-based SPT window estimates for dip calculation and the adherence requirements they impose. Finally, actigraphy-derived SPT windows do not represent ground-truth sleep periods. Additionally, SPT window estimation may be particularly challenging in populations with fragmented or atypical sleep-wake patterns, such as NT1. To mitigate this limitation, all automatically identified SPT windows in our study were reviewed by a researcher blinded to the ABPM data. Nevertheless, these limitations should be kept in mind when interpreting agreement between actigraphy-based dip estimates and those derived from the 24-h pattern and fixed-window approaches.

The three dip measures quantify BP and HR variability using different methodological definitions, so their values for a given participant are not directly comparable. However, the 24-h pattern dip values correlated more strongly with the actigraphy-based than fixed-window values, suggesting that the data-driven 24-h pattern approach may better account for natural between- and within-participant SPT window variability. Because Pearson correlation is sensitive to outliers and assumes a linear relationship, we note that it provides a limited view of agreement and should not be interpreted as a validation metric, but rather as a way to summarize relative ranking consistency across the three dip calculation methods.

Our data showed substantial variability in participants' average SPT start time (IQR 22:32 to 00:31 for the baseline ABPM visit). The within-participant variability was also substantial, with differences ranging from 4 to 27 min in sleep window start between baseline and week 3 ABPM visits. Although some of this variability may reflect natural differences in sleep timing, it may also be influenced by other factors like drug effect on sleep and daytime napping (out of scope for this analysis). Regardless of underlying factors, our results emphasize the need for methods of estimating BP and HR diurnal variability that address the between- and within-participant differences in true sleep time, as the 24-h pattern approach does.

In our sample, 61% and 41% of participants had fixed-window SBP and DBP dips <10%, respectively. The proportion of DBP non-dippers (41%) in our NT1 sample is higher than the 31% reported in drug-free individuals with NT1 by Dauvilliers et al. [5]. However, our analysis used a fixed-window approach, versus individually defined wake and sleep schedules, to determine dipping windows; these methodological differences limit comparability. Our results showed that the 30th percentile of DBP dip, close to the lowest third of the sample, varied substantially across dip calculation methods: 8.6% (fixed-window), 14.1% (24-h pattern), and 12.1% (actigraphy-based). This highlights how dip thresholds depend heavily on calculation methods. Moreover, DBP dips were consistently larger than SBP dips, meaning the proportion of non-dippers changed depending on whether the threshold was applied to SBP or DBP. Altogether, inconsistencies in defining daytime and nighttime windows, and ambiguity about whether the commonly used 10% threshold applies to SBP or DBP, hinder the comparability of non-dipping phenotype research. The definition of a "non-dipper" is hence not uniformly established and depends on the dip type (SBP or DBP) and calculation method. The 24-h pattern approach represents a step toward more robust quantifications of BP dipping by removing the need to define daytime and nighttime windows.

The two-component cosinor model mathematically allows for the presence of two dips in a 24-h cycle. We observed a "second dip" in 24-h patterns in a subset of participants: 23 (74%) for SBP, 18 (58%) for DBP, and 26 (84%) for HR. Although this pattern can simply reflect the model's flexibility, it might also represent the BP reductions associated with daytime nap episodes. Excessive daytime sleepiness, the cardinal symptom of NT1, commonly leads to daytime naps, and daytime napping is known to induce BP reductions [36]. For example, a daytime BP "mini-dip" during a siesta is well documented in populations where siesta is common [37]. Such reductions could lead to lowering of the daytime average BP and thereby decrease the calculated BP dip, introducing complexity to the interpretation of commonly used measures such as daytime average BP or

BP dip [37]. Future research could explore the influence of napping and other daytime behaviors on BP in NT1, and incorporate this information into a 24-h pattern approach.

In conclusion, dip values estimated using the data-driven 24-h pattern approach with two-component cosinor model for BP and HR were strongly correlated with actigraphy-based dip values, which utilized an objective algorithm to identify participants' sleep. In populations with sleep timing variations and disturbances, like NT1, the 24-h pattern approach offers a robust alternative to the fixed-window method for assessing dipping and does not require simultaneous actigraphy measurement. Classification of a "non-dipper" varies depending on the dip type and dip estimation method. We anticipate our findings on dip calculation approaches in individuals with NT1 to be replicable in other populations. We expect the 24-h pattern approach to be particularly useful in individuals with DNS, idiopathic hypersomnia, or irregular or extended sleep-wake patterns. Further research is warranted to evaluate these methods in other populations.

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Statement of Ethics

The TAK-994-1501 clinical trial protocol was reviewed and approved by the Institutional Review Boards or Ethics Committees at each participating site. The full list of participating site and Ethics Committees can be found in Dauvilliers et al. [23]. The trial was conducted in compliance with International Council for Harmonisation guidelines, the ethical principles outlined in the Declaration of Helsinki, and all applicable local or regional regulatory requirements. Written informed consent was obtained from all participants.

Conflict of Interest Statement

M.K., F.O., R.T., B.T., and D.V. are employees of Takeda Development Center Americas, Inc., and stockholders in Takeda Pharmaceutical Company Limited. L.B. received funds for travel to conferences from Bioprojet and Idorsia, and for board engagement from Bioprojet, Idorsia, Jazz Pharmaceuticals, and Takeda. Y.D. received funds for seminars, board engagements, and travel to conferences from Avadel, Bioprojet, Idorsia, Jazz Pharmaceuticals, Orexia, and Takeda.

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Author Contributions

M.K., F.O., B.T., and D.V. contributed to the conceptualization. M.K. conducted the formal analysis and wrote the original draft. D.V. supervised the work. M.K., F.O., R.T., L.B., Y.D., B.T., and D.V. contributed to the methodology, reviewed and edited the manuscript, and approved the final version for submission.

Data Availability Statement

The data that support the findings of this study are not publicly available due to sensitive participant information but are available from the corresponding author (M.K.) upon reasonable request.

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