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Nocturnal blood pressure measured by home devices: evidence and perspective for clinical application

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Studies using ambulatory blood pressure (BP) monitoring have shown that BP during night-time sleep is a stronger predictor of cardiovascular outcomes than daytime ambulatory or conventional office BP. However, night-time ambulatory BP recordings may interfere with sleep quality because of the device cuff inflation and frequency of measurements. Hence, there is an unmet need for obtaining high quality BP values during sleep. In the last two decades, technological development of home BP devices enabled automated BP measurements during night-time. Preliminary data suggest that nocturnal home BP measurements yield similar BP values and show good agreement in detecting nondippers when compared with ambulatory BP monitoring. Thus, nocturnal home BP measurements might be a reliable and practical alternative to ambulatory BP monitoring to evaluate BP during sleep. As the use of home BP devices is widespread, well accepted by users and has relatively low cost, it may prove to be more feasible and widely available for routine clinical assessment of nocturnal BP. At present, however, data on the prognostic relevance of nocturnal BP measured by home devices, the optimal measurement schedule, and other methodological issues are lacking and await further investigation. This article offers a systematic review of the current evidence on nocturnal home BP, highlights the remaining research questions, and provides preliminary recommendations for application of this novel approach in BP management.

Keywords: home device, night-time blood pressure, nocturnal blood pressure, self-measured home blood pressure, systematic review

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; BP, blood pressure; J-HOP, Japan Morning Surge-Home Blood Pressure; J-TOP, Japan Morning Surge-Target Organ Protection

INTRODUCTION

Home blood pressure (BP) measurement is widely used and well accepted by patients with hypertension for long-term use [1–3]. Home BP measurement is less cumbersome for patients than ambulatory BP monitoring [4]. Nonetheless, the self-measured home BP can be successfully used to detect white-coat and masked hypertension [5–8], is a stronger predictor of cardiovascular complications than BPs measured by clinicians in the office or clinic [6,8–10] (Supplemental Web Reference w1–w3, http://links.lww.com/HJH/B36), and improves long-term compliance with antihypertensive drug treatment [11] and hypertension control rates [12]. Home BP has become widely recommended for the management of hypertension as more values can be obtained over time away from the office setting and in the usual environment of each individual, and it reflects BP levels that are comparable to daytime average values [1–3,13].

Nocturnal BP obtained by ambulatory BP monitoring is a stronger predictor of cardiovascular outcomes than daytime (awake) ambulatory BP [14,15] (w4, http://links.lww.com/HJH/B36) or office BP [15,16] (w5 and w6, http://links.lww.com/HJH/B36]. The prognostic significance of the nocturnal BP has also been observed among patients with chronic kidney disease [17], patients with diabetes [18], and among adolescents and young adults with type 1 diabetes and microalbuminuria [19]. The outcome-driven threshold for nocturnal hypertension by ambulatory monitoring – corresponding to a conventional office BP of 140/90 mmHg – was reported to be 120/70 mmHg [20]; this threshold is

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widely supported by international guidelines [2,21]. Furthermore, a night-to-day ratio of BP level has prognostic value independently of the 24-h BP average. Additionally, a nondipping pattern (nocturnal 'systolic and/or diastolic' [22] BP fall of below 10% from the daytime values [13]) and a reverse dipping pattern (no reduction or increase in nocturnal BP [13], also referred to as an inverted dipper or riser pattern), are associated with increases in cardiovascular events and/or target organ findings [14,23,24] (w7–w11, http://links.lww.com/HJH/B36). In patients who are older [14,25], have diabetes [26], on antihypertensive drug therapy [14], have reduced kidney function [27] (w12 and w13, http://links.lww.com/HJH/B36), Cushing's syndrome [28], or are receiving glucocorticoid therapy [29], undergoing hemodialysis, or who have undergone renal [10] (w14, http://links.lww.com/HJH/B36) or cardiac transplantation [26], or have obstructive sleep apnea syndrome [30–32] (w15 and w16, http://links.lww.com/HJH/B36), the normal reduction in night-time BP is reduced or even reversed. Despite the major advantage of ambulatory BP in detecting varying patterns of circadian BP rhythm, night-time ambulatory BP recordings may interfere with sleep quality [13,33–37], making it difficult to accurately assess BP during sleep. Of additional concern is the impact of interrupted sleep on the reproducibility of nocturnal BP [7,38–42] (w17–w21, http://links.lww.com/HJH/B36).

Recent advances in self-monitoring device technology have enabled measurement of BP during night-time sleep [3,7]. The nocturnal home BP devices provides automated triggering of single or multiple nocturnal BP measurements. There is accumulating evidence that night-time home BP measurements are feasible and reliable [43–45] because of the development of accurate, low-cost and user-friendly devices [5]. This article presents a systematic review of the published evidence on nocturnal home BP measurement, considers the remaining research issues and puts forth recommendations for its clinical application.

Nocturnal home blood pressure

Definition

In the present article, the term 'nocturnal home BP' refers to the BP measured by home devices during the night. The ultimate purpose of home devices able to measure BP during the night is to capture accurate BP levels and their variations during the usual hours of night-time sleep. Concerning terminology in this field, we use the term 'nocturnal' measurement regardless of whether the individual is awake or asleep, unless otherwise specified, throughout this article. Moreover, as BP cannot be self-measured during sleep, the term 'self-measurement' for nocturnal BP does not mean that each nocturnal BP measurement is initiated by the patient. Thus, the measurement of the 'nocturnal home' BP in the current article is based on the decision of individuals themselves to undergo automatic BP measurements during sleep, regardless of whether they are asleep or awake at the time of measurement. Professional staff will typically instruct patients on how to prepare the device to take the measurements before retiring and to remove it after arising. A practical issue to address in this context is the optimal number of nocturnal BP readings to be scheduled, aimed at obtaining clinically valid information. For a more precise assessment, it would be preferable to record frequent measurements during sleep, but in doing so sleep may be interrupted in certain individuals. Thus, a reasonable compromise between the need for an accurate assessment of BP and keeping the interference of sleep quality to a minimum need to be reached.

Literature search

We searched the PubMed database using (night-time OR night-time OR asleep OR nocturnal) AND (home OR self-measured) AND 'blood pressure' AND ('1980/01/01' [Date – Publication]: '2017/09/30' [Date – Publication]) as initial search terms following the recent meta-analysis [43], in addition to eight publications by the authors, yielding 287 publications as shown in Fig. 1. After excluding a review and guidelines ($n = 59$), and limiting the search to articles in English ($n = 13$), 215 potentially relevant articles were extracted and these were fully evaluated independently by two investigators (T.F. and S.H.). Studies were eligible if they reported self-measured nocturnal home BP and were published as an original research study in a peer-reviewed publication. We excluded 204 articles because of the following reasons: studies were based on environmental measures, animal experiments, the same study population, or special population sample ($n = 47$), BP was not measured, or captured by ambulatory monitoring or clinic measurements only, with no data on nocturnal home BP monitoring ($n = 151$), studies reported incomplete data ($n = 5$), or nocturnal BP was measured at patients' house by an attendant ($n = 1$). We eventually identified 11 studies in which nocturnal home BP was measured, three of those were clinical trial. We have summarized the characteristics of these studies as shown in Table 1.

This systematic literature search revealed that there are few publications regarding nocturnal home BP measurements currently available. Furthermore, seven of the 11 selected articles came from Japan, the world's largest producing country of blood pressure monitoring devices [46]. Self-measured home BP has been widely accepted in Japan, and Japanese Guidelines emphasize the need of having home blood pressure measured in the morning and in the evening [2]. However, there may be a risk of bias, as results may differ according to population.

Studies on nocturnal home blood pressure

In 2001, the first data on a novel validated oscillometric upper-arm cuff home BP monitor (Omron HEM-747IC-N; Omron Healthcare Co., Ltd, Kyoto, Japan) equipped with a timer that triggered automated BP measurements during sleep were published by a Japanese research group [45]. After instruction by nurses on the home BP methodology, 49 patients set up the devices themselves before sleep. The devices automatically measured BP at the programmed clock time, 0200 h, and stored the readings on their memory chips. The next morning, after awakening, patients removed the device and documented in a diary whether the automated nocturnal BP measurement affected their quality of sleep. The average SBP of the patients increased in proportion to the degree of sleep disturbance according to a graded three-level sleep disturbance score, that is, 'no

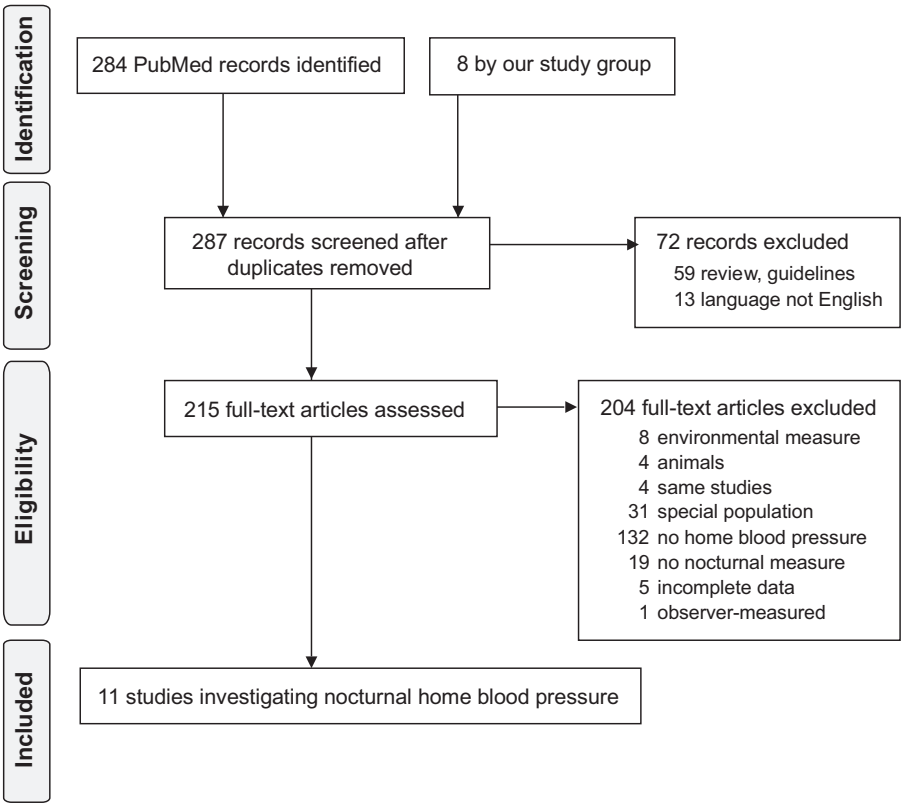

FIGURE 1 Flow diagram of selected studies.

sleep disturbance and no awareness of measurement,' 'mild sleep disturbance with an awareness of measurement,' and 'serious sleep disturbance' (from 116.1 ± 10.9 to 121.7 ± 15.5 mmHg; $P < 0.001$) [45]. The same research group later examined the reproducibility of nocturnal home BP [47] and reported that the correlation coefficients of the nocturnal measurements between two sessions using this method with an average interval of 5.9 days were modest

TABLE 1. Characteristics of studies investigating nocturnal home blood pressure

Authors (year)	Recruitment (country)	N° participants (% women)	Age, years (SD)	Device model (company)	Measurement days (intervals)	Measurements per night	SBP, mmHg	DBP, mmHg	Sleep quality assessment
Observational									
Chonan *et al.* (2001) [45]	HT (Japan)	49 (–)	–	HEM-747IC-N (Omron)	10 (1)	1 (0200 h)	118.6	72.8	At each post measurement
Hosohata *et al.* (2007) [47]	P (Japan)	556 (71)	62 (11)	HEM-747IC-N (Omron)	2 (6)	1 (0200 h)	116.8	68.0	At each post measurement
Ushio *et al.* (2009) [48]	V (Japan)	40 (30)	25 (5)	HEM-5041 (Omron)	7 (1)	6 (1 h interval)	107.6	59.3	After the measurement completion
Ishikawa *et al.* (2012) [49]	GP (Japan)	854 (53)	63 (11)	HEM-5001 (Omron)	9 (≥1 per wk)	3 (0200, 0300, 0400 h)	123.0	70.2	None
Stergiou *et al.* (2012) [58]	HT (Greece)	81 (47)	58 (11)	WatchBPN (Microlife)	3 (1)	3 (2, 3, 4 h after going to bed)	114.1	66.4	After the measurement completion
Stergiou *et al.* (2013) [30]	OSA (Greece)	39 (28)	49 (11)	WatchBPN (Microlife)	3 (1)	3 (2, 3, 4 h after going to bed)	115.1	69.3	Polysomnography
Andreadis *et al.* (2016) [59]	HT (Greece)	131 (42)	52 (12)	WatchBPN (Microlife)	3 (1)	3 (2, 3, 4 h after going to bed)	122.4	73.9	None
Lindroos *et al.* (2016) [60,72]	P (Finland)	248 (55)	58 (13)	WatchBP Home N (Microlife)	2 (1)	3 (2, 3, 4 h after going to bed)	113.0	65.2	After the measurement completion
Clinial trial									
Kario *et al.* (2010) [53]	HT (Japan)	161 (53)	67 (13)	HEM-5001 (Omron)	7 (1)	3 (0200, 0300, 0400 h)	131.6	75.7	None
Kario *et al.* (2017) [56]	HT (Japan)	411 (45)	63 (12)	HEM-7252G-HP (Omron)	5 (1)	3 (0200, 0300, 0400 h)	128.3	79.3	None
Fujiwara *et al.* (2018) [55]	HT (Japan)	129 (57)	68 (12)	HEM-7252G-HP (Omron)	3 (during 4 wk)	3 0200, 0300, 0400 h)	125.1	76.3	None

(–), not available; BP, blood pressure; GP, patients from outpatient clinic; HT, patients with hypertension; OSA, patients with obstructive sleep apnea; P, general population; V, healthy volunteers; wk, week. When two or more articles were published from the single study, we extracted data from the initial report.

($r = 0.67/0.55$ for SBP/DBP) and standard deviations (SDs) of the BP differences were large ($\geq$13.6/$\geq$9.3 mmHg), despite taking into account the degree of sleep disturbance; it may be partly because the BP was measured only once, at 0200 h, per session. Subsequently, Ushio *et al.* [48] reported that another home device (Omron HEM-5041) provided estimates of the nocturnal BP in Japanese healthy volunteers similar to those measured by nocturnal ambulatory BP monitoring [5].

In the Japan Morning Surge-Home Blood Pressure (J-HOP) study [49,50], nocturnal home BPs were measured at three preset times per night at 1-h intervals, that is, at 0200, 0300, and 0400 h [49,50]. In the initial J-HOP report [49], the nocturnal home BP over an average of 8.9 ± 4.3 nights (25.5 ± 12.7 readings) was the lowest at 0200 h and increased at 0300 h and again at 0400 h. The significant increase in BP at 0400 h was confirmed by a J-HOP's later report on 2562 patients [50]. A similar trend was observed in the ambulatory BP measurements of 854 patients obtained using the validated oscillometric devices A&D TM-2421 [51] and A&D TM-2425 [49] (A&D Co. Inc., Tokyo, Japan). Although the nocturnal home SBPs and DBPs were 2.1–3.2 mmHg higher and 0.5–0.8 mmHg lower, respectively, than ambulatory BPs measured at the same time points [49], these differences were within the range of error of oscillometric BP values obtained by ambulatory devices [52].

The J-HOP study group simultaneously conducted the Japan Morning Surge-Target Organ Protection (J-TOP) trial in which the nocturnal home BP was measured under the same protocol as the J-HOP study [53]. On the basis of this first nocturnal home BP-based clinical trial on antihypertensive medication received either at bedtime or upon awakening, a significant reduction in the nocturnal home BP of the 161 participants was observed during 6-month (from 6.4 to 8.8 mmHg and from 3.1 to 5.3 mmHg for SBP and DBP, respectively) [53]. This reduction did not differ between home and ambulatory BP measurements within a subgroup of 50 patients, regardless of the time of drug administration (systolic/diastolic: $P = 0.22/0.34$) [54]. However, the individual patient measurement plots demonstrated wide differences between home and ambulatory BP values both in the systolic (mean $\pm$ 2 SD; -35.5 to $+29.8$ mmHg) and diastolic (-25.3 to $+22.1$ mmHg) measurements [54]. The nocturnal home BP technology has also been applied to drug therapy studies in hypertension [55,56]. Using the same schedule of three fixed measurements per night, the reduction of the nocturnal BP during 8 weeks of combination therapy with irbesartan with amlodipine was found to be significantly greater than that in patients who received irbesartan with trichlormethiazide (14.4/7.3 versus 10.5/5.6 mmHg, respectively; $P \leq 0.0056$) [56].

The Microlife WatchBPN device (Microlife Corp., Widnau, Switzerland) also enables automated monitoring of nocturnal home BP [57]. A research group in Greece performed a pilot study using the Microlife WatchBPN device in 39 patients referred to a sleep clinic and showed nocturnal home BP to be correlated with indices of obstructive sleep apnea severity [30]. The same investigators used the WatchBPN home monitor and the Microlife WatchBP O3 ambulatory monitor in 81 patients with hypertension and showed similar night-time BP values with the two methods, as well as substantial agreement between them in detecting nondippers [58]. It is notable that both WatchBP O3 and WatchBPN use the same oscillometric BP measurement algorithm, which minimizes the systematic error caused by using a different device for each method (home and ambulatory), and therefore the net BP difference between the two methods could be demonstrated in the study. The same group further reported that in 131 untreated patients with hypertension, nocturnal home BP was a significant determinant of left ventricular mass index, carotid intima–media thickness, and urinary albumin excretion ($P \leq 0.01$), and the determination coefficient R^2 of each multivariable model was 0.26, 0.25, and 0.28, respectively [59]. These findings were corroborated by a Finnish study using the same ambulatory (Microlife WatchBP O3) and home (WatchBP Home) devices for nocturnal BP evaluation in a 248 subject cohort, in which multivariable-adjusted models showed the nocturnal home BP to be significantly associated with pulse wave velocity, intima–media thickness, and left ventricular mass index ($P \leq 0.003$) except the diastolic value with intima–media thickness ($P = 0.13$) [60].

Nocturnal ambulatory versus home blood pressure

Reproducibility

Individual values of average ambulatory BP have shown a moderate correlation between two monitoring sessions ($r = 0.56$ and 0.82 for systolic, and $r = 0.51$ and 0.79 for diastolic), as reported by Keren *et al.* [38] and Ash *et al.* [39], respectively. The reproducibility of average 24-h, daytime, and night-time ambulatory BP is better than that of average hourly values and much better than that of office BP readings [42,61]. Of note, the reproducibility of clinic BP in the outpatient setting has been reported to be increased by averaging repeated BP measurements as they occur in day-by-day BP monitoring [62]. Among untreated patients with hypertension, the test–retest correlation coefficients of awake and sleep ambulatory monitoring of the SBP/DBP were 0.74/0.80 and 0.81/0.79, respectively [63]. The SD of the differences were 10.0/6.6 mmHg for awake, and 9.2/7.0 mmHg for sleep ambulatory BP [63]. Physicians should thus be cautious about clinical decision-making based on short ambulatory BP measurement periods. Reproducibility of self-measured home BP was comparably high between two sets of 2-day measurements (days 2–3 versus 4–5; correlation coefficients, 0.91/0.86 in SBP/DBP; SD of differences, 6.9/4.7 mmHg) [63], and even between two sets of measurements taken at a 1-year interval (correlation coefficients, 0.84/0.83; SD of differences, 7.7/5.5 mmHg) [64].

Although no direct comparison between the reproducibility of nocturnal ambulatory and home BP has been published, it should be emphasized that, at variance from the good reproducibility of the average of a consistent number of nocturnal BP monitoring [42], the reproducibility of a few night-time BP readings is imperfect regardless of whether it is determined by ambulatory [65] or home measurements [45,47]. Eguchi *et al.* [66] reported similarly low reproducibility between two pairs of two sleeping BP readings, regardless of whether the patients received

antihypertensive drugs (SD of the difference: 13.0/7.9 mmHg for SBP/DBP before the initiation of treatment, and 15.0/8.3 mmHg on-treatment) in comparison with measurements recorded while the patient was awake (12.1/6.6 and 14.6/8.5 mmHg). The reproducibility of the circadian BP pattern and the amplitude of the nocturnal fall of BP were also relatively poor [40–42] (w17–w21, http://links. lww.com/HJH/B36); however, during long-term observation, the nocturnal BP dip was essentially stable over time when expressed as a continuous variable [67]. A repeated nondipping pattern at two different 24-h ambulatory monitoring sessions has been determined to better reflect cardiac abnormalities than a single monitoring session [68], whereas day-to-day nocturnal dipping patterns can be influenced by sleep quality [41]. However, in the clinical setting, repeated monitoring of the nocturnal BP in diverse populations is rarely performed by 24-h ambulatory recording. Thus, in conclusion, the reproducibility of BP readings, regardless of whether self-measured at home, recorded during ambulatory BP monitoring, or obtained in the office during consultation, deserves attention by clinicians as it has demonstrated important associations with cardiovascular outcomes.

Patient preference

The clinical usefulness of BP measurement relies on the commitment and preference of the people in need of these measurements. Overall acceptance and preference by patients with hypertension were reported to be better for home BP measurement compared with ambulatory BP monitoring [69,70]. These findings were independent of potential characteristics of patients, including previous experience with BP measurement [69]. In addition to nocturnal BP measurement, typical reasons for preferring 7-day home measurement over 24-h ambulatory monitoring included the ability to instantly see BP values, a sense by participants that they were more 'in control,' and less embarrassment or awkwardness because ambulatory BP measurements sometimes occur in public spaces [70]. Conversely, one of the perceived benefits of ambulatory BP monitoring was the shorter duration of the monitoring period (only 1-day) [70]. Interestingly, on the day of ambulatory recording, patients were sedentary for an average of 27 min longer during waking hours than they were on nonrecording days ($P = 0.002$) [71]. Moreover, nocturnal ambulatory BP monitoring has been associated with a progressive increase in perceived sleep deprivation in comparison with days without ambulatory BP monitoring ($P < 0.01$) [33]. Both reports [33,71] support the general concern that ambulatory BP monitoring may not always capture the 'real' BP of an individual. Despite the many advantages of ambulatory BP monitoring, excessively frequent cuff inflations cause disruption of sleep, resulting in reduced adherence of patients to repeat the measurements [13]. Recent studies suggest that home BP measurement, particularly nocturnal measurement, is at least as well accepted as ambulatory monitoring, with a trend towards less-severe sleep disturbance [43,48,58,72]. However, the preferences of patients with regard to the number of home BP measurements per night is still not known because different schedules of nocturnal home BP measurements and different questionnaires for assessing patient preferences have been used [48,58,72].

Cost effectiveness

Evidence is accumulating regarding the possibility of cost savings with out-of-office BP compared with conventional clinic BP measurement [73]; however, no cost-effectiveness analysis on nocturnal home BP has yet been reported at this emerging stage of the method. Ambulatory BP monitors are generally much more expensive than currently available home BP-measuring devices, most of which cost less than 100 Euros. Although clinicians can evaluate hundreds of patients by using the same ambulatory BP monitor, an individual low-cost home BP device enables us to repeatedly measure BP in the daily life of each person. Moreover, the widespread clinical application of home devices is now being further favoured by currently developing technologies for remote telemonitoring and telemedicine [55,56,74]. For this very reason, nocturnal home BP has the potential to avoid the limited application of nocturnal BP measurement by ambulatory monitoring. Nevertheless, we cannot ignore the initial cost of introducing home devices to each patient.

Association with target organ damage

In a recent meta-analysis [43], nocturnal home and ambulatory BP measurements were found to be similarly associated with indices of target organ damage (i.e. left ventricular mass index [49,59,60] and common carotid intima–media thickness [59,60]). In this meta-analysis, nocturnal home BP was superior to nocturnal ambulatory BP in its relationship to urinary albumin excretion ($P < 0.01$ for comparison) [43]. However, the results [49,59] were from only two studies. Hence, there are still insufficient data comparing the predictive values for target organ damage of nocturnal home and ambulatory BP, and even less is known in relation to cardiovascular events. With regard to pulse wave velocity, Lindroos *et al.* [60] reported a stronger correlation with nocturnal ambulatory BP than with nocturnal home BP ($r = 0.57$ versus $r = 0.50$; comparison $P = 0.03$). In contrast, a similar correlation with ankle–brachial index was reported for nocturnal DBP when comparing ambulatory BP ($r = 0.23$) and home BP ($r = 0.29$) [59], whereas the correlation with ankle–brachial index was similarly poor for nocturnal SBP ($r = 0.04$ for ambulatory; $r = -0.01$ for home) [59]. In relation to hard cardivascular outcomes, which should be the ultimate criterion for considering the usefulness of exposures, available data suggest that nocturnal home BP might have similar prognostic ability compared with nocturnal ambulatory BP; but appropriate outcome studies are needed.

Features of nocturnal home blood pressure measurement

The measurement device

Recent guidelines [1–3,10,21] recommend the use of a validated upper arm cuff oscillometric devices for home BP measurement, and in all the aforementioned studies nocturnal home BP has been measured based on validated upper arm cuff devices (Table 1). An upper arm-cuff is generally well aligned with the heart level regardless of

whether patients are sitting, standing, or lying on their back [75]. It would be appropriate to follow the same recommendation when undertaking nocturnal home BP measurements. Furthermore, as one cannot watch a nocturnal measurement during sleep, adequate instruction for the user on the nocturnal home BP methodology by professional staff, including how to fit and remove the device, is highly recommended.

Wrist-cuff oscillometric BP measurement devices have been marketed and widely used in clinical practice, particularly for self-measurement of BP during daytime. Such devices may be acceptable in limited situations, for example, day-to-day monitoring during travel, patients with arm circumferences that are too large or where the upper arm length is too short to apply a large cuff [21], or – as described later – to measure nocturnal BP during sleep. The measurement-induced reactive rise of home BP values by a wrist-cuff device was reported to be smaller than that by an upper-arm cuff device in hypertensive patients [76] as the wrist-cuff device may cause less discomfort and muscle compression [77]. Nevertheless, there are some problematic aspects related to use of the wrist-cuff devices. One problem is the hydrostatic height-related pressure difference between wrist and heart levels in the lying posture during sleep; a 10-cm hydrostatic pressure difference between the heart level and cuff position results in a 7-mmHg difference in BP levels [78,79]. Even when patients remain in the lateral recumbent position during sleep, the difference in the position between the level of the heart and the mid-arm level is less than that at the wrist level. Another limitation of wrist devices is the different accessibility of radial and ulnar arteries by the device in different people, because of individual anatomical characteristics of the wrist [3,78]. Although wrist position sensors help patients to self-measure their wrist BP more accurately while they are awake [79], there is no guarantee that even the most advanced wrist-cuff oscillometric device will measure the nocturnal BP accurately during sleep – at least to the level of precision seen with validated upper arm-cuff devices.

Measurement schedule and conditions

Recent studies have used three preset measurements per night [49,53,56], at fixed times of 2, 3, and 4 h after going to bed [30,58–60,72], up to six measurements per night at 1-h intervals [48], or one preset measurement per night with a questionnaire on sleep quality [45,47]. A meta-regression analysis revealed that the differences between home and ambulatory BP was not significantly affected by the number of nocturnal home BP readings [43]. The same research group recently proposed a two-night home BP schedule with three-hourly automated measurements each night as a minimum requirement for the reliable assessment of nocturnal home BP [44]. This proposal is based on a cross-sectional study that included 94 untreated patients with clinic hypertension ($\geq$140/$\geq$90 mmHg on outpatient office measurement) [59] to assess the correlation coefficients between target organ damage and nocturnal home/ambulatory BP, and the diagnostic agreement between home and ambulatory BP in detecting nondippers and patients with nocturnal hypertension when ambulatory monitoring was set as reference method [44].

The major advantages of nocturnal home BP measurement include that it allows the participants' quality of sleep to be self-reported [45] and that it enables us to easily obtain a periodic recording of nocturnal BP. Although more research is needed on the quality of sleep during nocturnal BP recordings, a single nightly measurement repeated over a relatively long period (e.g. 5 days [2], 7 days [21], or much longer) can yield highly reliable sleep BP measurement values as documented by sleep quality questionnaire administered on the night of the BP recording. Just as the daily recording of morning/evening home BPs can reveal the time of the maximal effect (stabilization time) of antihypertensive treatment [80], the periodic measurement of the nocturnal home BP may have additional clinical value as it may allow to assess the long-term BP-lowering effect at night of antihypertensive drug therapy [11,80] and seasonal variations in nocturnal home BP levels [81,82].

Measuring nocturnal home BP for even just one night, which is the usual approach when using ambulatory BP monitoring, can capture basic information on nocturnal BP level associated with comparably accurate information on quality-of-sleep self-reported over the nocturnal measurement period [45]. This approach does not take advantage of the strengths of multiple nocturnal home measurements, however. The number of nocturnal home BP measurement varied among previous studies (Table 1), and further research is needed to specify optimal nocturnal home BP measurement schedules according to the purpose for which they are performed, including the preference of patients for the frequency of the measurement. This issue must remain open until robust evidence on nocturnal home BP becomes available.

Conditions that may affect the nocturnal home BP are listed in Table 2. Although daytime activities such as

TABLE 2. Factors potentially affecting nocturnal home blood pressure

Lifestyle
Exercise before going to bed
Heavy evening meal
Excessive alcohol consumption prior to retiring
Too much fluid consumption prior to sleep or during night
Insufficient sleep time
Poor quality of sleep
Smoking in the evening
Obese/overweight
Environmental factors
Room temperature (season, air conditioning)
Weekday/holiday versus workweek
Room lighting and sound
Spouse/children in the same bed/room
Measurement devices and conditions
Type of device (wrist versus upper arm-cuff, degree of noise, etc.)
Cuff size/position
Number of measurements per night
Cuff inflation/deflation time and noise
Clinical factors
Blood volume status
Secondary hypertension
Autonomic neuropathy
Personality/psychological state (anxiety, depression)
Cognitive function (disorientation during sleep)
Poor quality of sleep (including sleep apneas-hypopneas)
Cardiac or renal transplantation, renal denervation
Use of antihypertensive drugs at night
Use of sedative/hyponotic medications
Cerebrovascular disorders

smoking, alcohol, and caffeine consumption also affect BP during sleep, the nocturnal home BP offers the advantage of being measured in a relatively controlled condition. Whereas, activities before going to bed along with dietary habits including salt intake — which may be affected by salt sensitivity in individuals [83] — can be influential factors to affect nocturnal BP. In case of nocturnal home BP measurement, healthcare providers should ask participants to record their activities in a diary, along with the nocturnal home BP values, and should refer to the information in the diary to help guiding clinical decision-making. For research purposes as well as in clinical practice, the use of specific devices (e.g. to self-monitor urinary sodium-to-potassium ratio [84] for the estimation of sodium intake) may be helpful to identify possible factors involved in determining the BP rise associated with nocturnal home measurement. It is also recommended that sleep quality be recorded by means of self-reporting [45], applying actigraphy [37] or other methods insofar as possible.

Diagnostic usefulness and thresholds for treatment of hypertension

A recent meta-analysis [43] revealed that the nocturnal home and ambulatory BP measurements provide similar values (home measurements were 1.4 mmHg higher for systolic (95% confidence intervals, 0.3–2.6) with no significant difference for diastolic values (−0.2 mmHg; 95% confidence intervals, −0.9 to 0.6] in comparison with ambulatory BP measurements; Fig. 2). Because of this small difference in the BP levels [43], the definition of

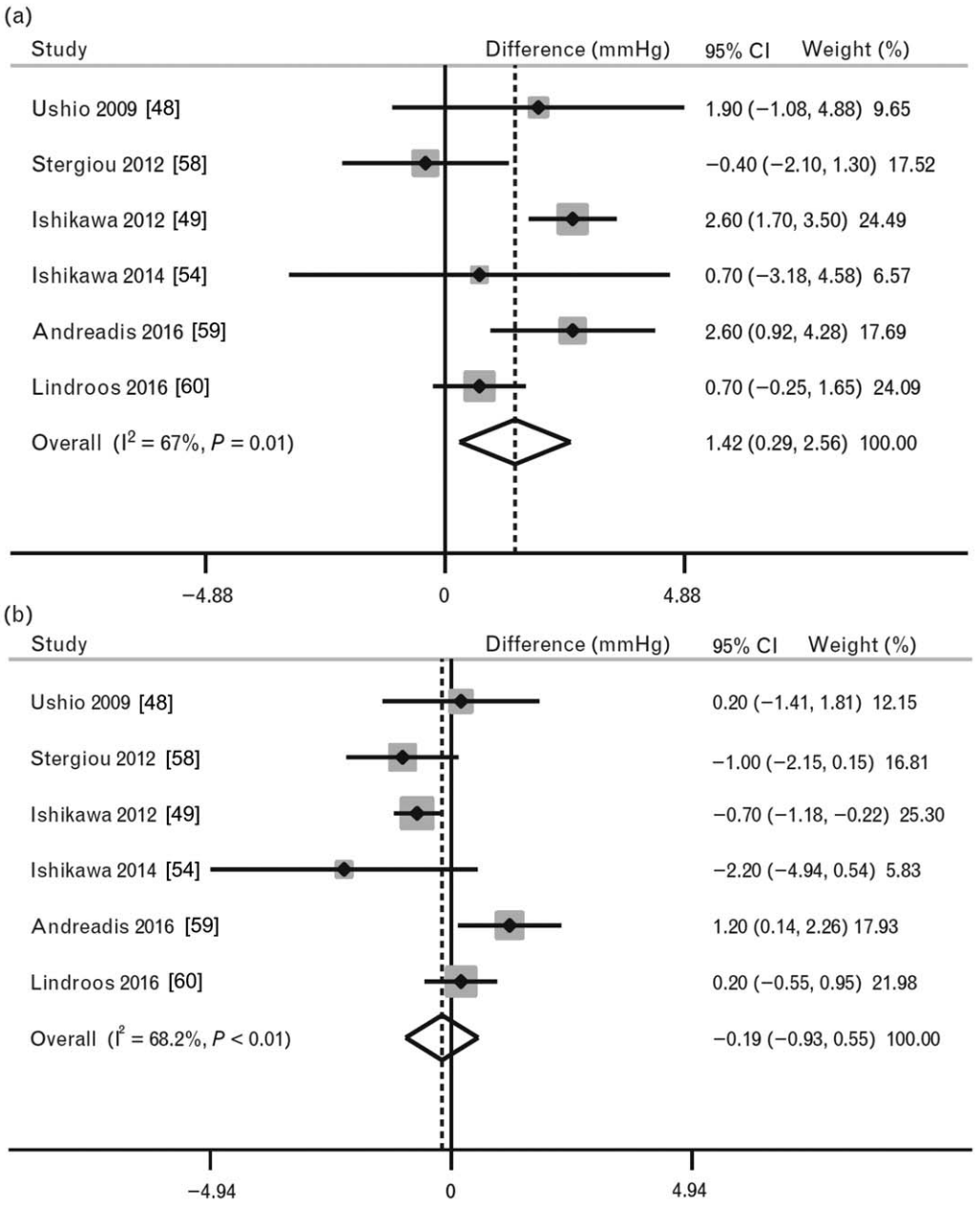

FIGURE 2 A forest plot of the pooled differences in nocturnal home minus ambulatory blood pressure. (a) SBP. (b) DBP. CI, confidence intervals. Reproduced from Kollias *et al.* [43].

hypertension based on nocturnal home BP should not be different from the definition of hypertension based on nocturnal ambulatory monitoring, that is a mean nocturnal BP of at least 120 mmHg/at least 70 mmHg [2,21], which corresponds to a clinic BP of at least 140 mmHg/at least 90 mmHg as a population [20].

The 2017 ACC/AHA Hypertension Guidelines in the United States estimated that a nocturnal ambulatory BP level of at least 110 mmHg/at least 65 mmHg corresponded to the new recommended definition of stage 1 hypertension (≥130/≥80 mmHg by conventional clinic BP measurement) although such an estimate is not outcome-based [1]. Thus, the suggestion to consider people with nocturnal home BP of at least 110 mmHg/at least 65 mmHg as having nocturnal home hypertension under this revised office BP threshold [1] would need to be further evaluated in the light of additional evidence derived from future studies. Taking the recent publications on nocturnal ambulatory BP monitoring [2,20,21,85] into consideration, the diagnostic threshold of nocturnal home hypertension as at least 120 mmHg/at least 70 mmHg remains reasonable for most patients.

Given that the recommended threshold for daytime ambulatory BP is the same as for home BP and that nocturnal home BP levels appear to be similar to nocturnal ambulatory BP, home BP measurement might be a useful and practical alternative to ambulatory BP monitoring in detecting participants with nondipping patterns. Furthermore, three studies reported the agreement between home and ambulatory BP in detecting nondippers to range from 74 to 79% [44,58,59], which is similar to the test–retest reproducibility of repeated ambulatory BP monitoring in detecting nondippers [40,67]. The reported similarity between the home-ambulatory BP agreement [44,58,59] and the agreement between repeated ambulatory BP monitoring in diagnosing a nondipping BP pattern [40,67] also implies that the ambulatory and home BP might be regarded as interchangeable approaches in the detection of nondippers.

Effect of cuff inflation on blood pressure levels during sleep

Cuff inflation and sleep quality

Despite the major role that nocturnal ambulatory BP has gained in predicting cardiovascular risk, an important problem remains that the measurement of BP affects sleep quality. The effect on sleep quality is mainly attributed to the disturbance of sleep by cuff inflation. As shown by studies, which combined polysomnography or electroencephalography with nocturnal BP monitoring, cuff inflation was associated with increased arousal and wakefulness [86]. Davies *et al.* [34] reported that the mean duration of arousal by ambulatory measurement during sleep was 8–16 s. The BP recording procedure caused a tiny but significant decrease in the slow-wave sleep period and an increase in nocturnal awakening [87]. Brazilian investigators reported that 35.1% of patients had an abnormal sleep quality on the day of 24-h ambulatory BP monitoring [88]. Furthermore, 24-h ambulatory monitoring sometimes causes adverse effects such as pain, skin irritation including upper-arm ecchymoses, and disruption of work [89]. A questionnaire-based sleep quality assessment revealed that 61% of patients undergoing nocturnal ambulatory BP monitoring reported a minor disturbance of sleep, 14% had poor sleep, and 2% did not sleep at all [89]. According to French cardiologists, severe difficulty (defined as ≥3 instances of disturbance by the device during 24-h measurement) occurred in 32% of their patients in relation to cuff pressure, whereas 14% reported that it was cumbersome [90]. As a consequence, 45% of the patients reported experiencing a sleeping delay, 36% reported arousal, and 14% reported lower sleep quality. Moreover, a remarkable 95% of patients who did not sleep alone reported that it disturbed their spouse's sleep as well [90]. More than half (58%) of the participants recalled cuff inflation during the nocturnal ambulatory monitoring [86].

Cuff inflation and nocturnal blood pressure

Investigators have reported an inverse association between BP levels and sleep quality. A lower BP was significantly associated with deeper sleep [34,35]. Although the sleep stage was not changed on electroencephalography, arousal stimuli produced a significant increase in BP (8.6 mmHg in SBP) [36]. A recent report by Oume *et al.* [37] also supported this association based on the actigraphic sleep parameters of 1127 residents aged at least 60. It is, therefore, a reasonable assumption that cuff inflation induces an increase in BP. Heude *et al.* [91] reported that upper arm-cuff inflation itself raises the nocturnal BP, even when a carbon dioxide cartridge is used to inflate the cuff silently. In recent studies by Sheshadri *et al.*, the mean changes in the invasive arterial SBP/DBP level among 97 patients during each of six contralateral arm-cuff inflations were $6.7 \pm 5.9/2.6 \pm 4.0$ mmHg [92]. SBP increases of 0–10 mmHg were observed in 73.4% of cuff inflations, which was independent of the baseline BP levels [92]. Interestingly, despite the fact that two-thirds of BP measurements caused arousal evaluated by simultaneous electroencephalography, neither the average SBP (1.2 ± 6.4 mmHg) or DBP (0.5 ± 4.1 mmHg) BP levels differed to a statistically significant extent between the uninterrupted sleep and the arousal period [35]. The addition of noninvasive automatic or semiautomatic BP monitoring did not cause any alterations in the day and night intra-arterial BP or heart rate profiles in a few studies by the Milan group [93–95]. Studies on Brazilian patients [88] and Danish diabetes patients [96] supported the absence of an association between arm-cuff inflation and BP levels, too. However, it is worth noting that bedside monitoring with a catheter represents a different condition from the usual ambulatory setting, although the studies carried out in Milan were based on 24-h intra-arterial ambulatory BP monitoring. There might be some individual variability in the degree of BP rise triggered by arm-cuff inflations, and that arm-cuff inflation causes a transient reactive increase in BP in some individuals and that the averaging of the nocturnal BP values could mask the elevation that occurs at the precise moment of BP during arousal or cuff inflation.

Pump-inflation noise and nocturnal blood pressure

There are technologic advances in BP device pumps to limit noise during cuff inflation. For example, an innovative,

upper arm-cuff inflated by an electric motor drive unit that produces low noise cuff inflation of 36.7–41.5 dB has recently been developed (communication from Research and Development section, Omron Healthcare Co., Ltd). This is a noise considered to slightly more than a whisper (≈35 dB) or the background noise in a public library (≈40 dB). This device is nearly as quiet as the ABPM-630 (Nippon Colin, Komaki; currently Fukuda Colin, Tokyo, Japan) [16,91,97] which provided silent inflation; but because of the frequent exchange of a carbon dioxide gas cartridge required for this device, it became impractical and has been discontinued from clinical commercial use. It is also noteworthy that wrist-cuff devices usually generate less noise because of its small bladder size; for example, the wrist-cuff oscillometric HEM6310F-N (Omron Healthcare, Co., Ltd) produces a noise of only 8.1–18.0 dB (communication, Research and Development section, Omron Healthcare Co., Ltd). This quiet measurement condition further favors an accurate measurement of BP during the cuff inflation phase [98] as it does not cause the usual loud noise by upper arm-cuff devices that compromises an accurate oscillometric signal capturing during cuff inflation. A wrist-cuff device may represent a favorable solution for nocturnal home BP measurement with minimal disruption of sleep, an issue which needs to undergo adequate investigation, together with other abovementioned crucial features characterizing wrist-cuff devices for nocturnal BP measurement.

Miscellaneous issues related to nocturnal home blood pressure

In the clinical setting – as opposed to the research setting – there is room for debate on how to define sleep because of the difficulties in obtaining accurate documentation. The use of the standard narrow-fixed clock intervals with ambulatory BP monitoring, that is, defining the time periods 0900–2100 h as daytime and 0100–0600 h as night-time, has allowed to define the prognostic significance of a rising pattern in nocturnal BP (hazard ratio, 1.57; 95% confidence intervals, 1.08–2.27 in comparison to participants with a dipping pattern) [99]. However, diary record-based classifications provided the best predictive power for stroke incidence (hazard ratio 2.31; 95% confidence intervals, 1.47–3.62) [99]. The recall of subjective sleep disturbances during nocturnal home BP measurement [45,47] would be a feasible option to investigate interference with sleep quality, although this approach does not guarantee whether an individual actually remained asleep during the measurement. Given the evidence that the quantity and quality of sleep predict cardiovascular outcomes [100,101], sleep per se has been indicated as area of interest, together with nocturnal BP, for research in cardiovascular prevention. Hence, there is a need for a convenient and widely available method of determining the state of sleep during BP measurement. Actigraphy has been used for decades as a tool to screen the state of sleep and to identify people who might benefit from a more precise diagnostic approach through polysomnography [102], that is applicable to either patients [66] and general population [37].

Specific event-triggered BP measurement, such as at the peak of hypoxemia in patients with obstructive sleep apnea patients [31,103,104] or at the time of the lowest heart rate that may coincide with low levels of sympathetic nervous system activity [105], would be approaches worth considering for research, aimed at improving the clinical relevance of nocturnal home BP measurement. Such measurements can capture specific episode-related sleep BP surges or declines and may reduce the number of BP readings required during sleep [106,107]. Moreover, a night-time home BP telemonitoring system has become available by recently marketed devices, such as the Omron HEM-7252G-HP, in which a mobile communication facility is embedded [55,56,74]. Continuous research and development into new home BP devices will enhance the usefulness of night-time home BP measurement in the near future [107].

TABLE 3. Potential research areas for future studies on nocturnal home blood pressure

Comparisons with ambulatory blood pressure monitoring
Reproducibility and reliability
Preference by patients
Cost-effectiveness
Improvement of technical aspects of measurement devices
Cuff performance
Pump noise
Measurement schedule and conditions
The accurate evaluation of sleep quality
Factors affecting nocturnal home blood pressure[a]
Association with organ damage
Prognostic impact
Cardiovascular/cerebrovascular disease
Renal outcomes
Functional outcomes in older persons (cognition, mobility and balance)
Diagnostic usefulness
Thresholds for treatment

[a]See Table 2.

CONCLUSION

In the last two decades, technological advancement in home BP devices have allowed the evaluation of BP also during night-time sleep [7,43]. Preliminary evidence shows that nocturnal home BP measurement is feasible and provides levels of nocturnal BP and ability to detect nondippers similarly as ambulatory BP monitoring does. Thus, nocturnal home BP measurement might be a practical and reliable alternative to ambulatory BP monitoring, which has been indicated as the gold standard for out-of-office BP measurement but has been limited in its dissemination by practical and economic concerns [5]. Subheadings of the present article represent possible items of a research agenda for future studies on nocturnal home BP (Table 3), among which associations of nocturnal home BP with cardiovascular outcomes are most important. These research data are needed to guide the implementation of nocturnal home BP measurement in the management of patients with hypertension in clinical practice.

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Conflicts of interest

Y.I., T.O. and K.K. received research grants from Omron Healthcare. KA., T.O., K.K., and M.A.W. are consultants for Omron Healthcare. K.K., G.S.S., G.P., and Y.I. conducted validation studies for various manufacturers and advised manufacturers on device and software development. The other authors declare no conflicts of interest in association with the present study.

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