Objectives: Errors in blood pressure (BP) measurement account for a large proportion of misclassified hypertension diagnoses. Ambulatory blood pressure monitoring (ABPM) is often considered to be the gold standard for measurement of BP, but uncertainty remains regarding the degree of measurement error. The aim of this study was to determine reproducibility of sequential ABPM in a population of normotensive and well controlled hypertensive individuals.

Methods: Individual participant data from three randomized controlled trials, which had recorded ABPM and carotid-femoral pulse wave velocity (PWV) at least twice were combined (n = 501). We calculated within-individual variability of daytime and night-time BP and compared the variability between normotensive (n = 324) and hypertensive (n = 177) individuals. As a secondary analysis, variability of PWV measurements was also calculated, and multivariable linear regression was used to assess characteristics associated with blood pressure variability (BPV).

Results: Within-individual coefficient of variation (CoV) for systolic BP was 5.4% (day) and 7.0% (night). Equivalent values for diastolic BP were 6.1% and 8.4%, respectively. No statistically significant difference in CoV was demonstrated between measurements for normotensive and hypertensive individuals. Within-individual CoV for PWV exceeded that of BP measurements (10.7%). PWV was associated with mean pressures, BMI for night-time measurements. PWV was not independently associated with BPV.

Conclusion: The variability of single ABPM measurements will still yield considerable uncertainty regarding true average pressures, potentially resulting in misclassification of hypertensive status and incorrect treatment regimes. Repeated ABPM may be necessary to refine antihypertensive therapy.

Graphical abstract: http://links.lww.com/HJH/C100.

Keywords: ambulatory, ambulatory blood pressure monitoring, blood pressure, hypertension, reproducibility

Abbreviations: ABPM, ambulatory blood pressure measurement; ANOVA, analysis of variance test; BP, blood pressure; BPV, blood pressure variability; CI, confidence interval; CoV, coefficient of variation; IPD, individual patient data; PWV, pulse wave velocity; RCT, randomized controlled trial; SD, standard deviation

Original Article

Reproducibility of sequential ambulatory blood pressure and pulse wave velocity measurements in normotensive and hypertensive individuals

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INTRODUCTION

Ambulatory blood pressure measurement (ABPM) has been shown to be the most cost-effective option to confirm a diagnosis of hypertension [1]. The reproducibility of average blood pressure (BP) taken by 24-h ABPM has been previously shown to be superior to the reproducibility of clinic BP [2–4]. However, the majority of studies examining ABPM reproducibility have been performed with time intervals of 12 weeks or less, or in individuals with long-term hypertension or a history of cardiovascular disease.

There are fewer studies comparing techniques for long-term monitoring and clinic BP remains a first-line tool despite well known risks from white-coat or masked hypertension [5–7]. Long-term monitoring using ABPM could facilitate improved BP control, but the degree of variability between sequential ABPM in normotensive and stable hypertensive individuals otherwise free from overt cardiovascular disease is poorly characterized.

A retrospective analysis of individual patient data (IPD) from randomized controlled trial (RCTs) provides an opportunity to investigate ABPM measurement variability. Here, we present analyses of measurement variability from three studies, which investigated possible benefits of dietary modification on ambulatory BP and arterial stiffness in individuals who were normotensive or with well controlled hypertension [8–10]. The concurrent measurement of pulse wave velocity (PWV) in these individuals presented an ideal opportunity to directly compare the reproducibility of PWV against that of ABPM, as superior reproducibility may...
support the alternate use of PWV as a long-term monitoring tool for cardiovascular health.

Even in a healthy population, reproducibility of BP measurements will be affected by blood pressure variability (BPV). Some degree of BPV is a normative property, but a high variability has been shown to be associated with an increased risk of cardiovascular outcomes, independent of the mean systolic pressure [11–13]. Determinants of increased BPV may include general cardiovascular risk factors such as increasing age, arterial stiffness and adverse lipid profiles [14,15] amongst others. Elucidation of factors associated with BPV in this cohort may provide clues to modifiable risk factors for high BPV in cohorts at a higher risk of cardiovascular morbidities.

Therefore, the primary aim of the present study was to calculate reproducibility associated with sequential ABPM in this relatively healthy population of normotensive and well controlled hypertensive individuals. Secondary aims were to estimate BPV and its potential determinants and to compare the reproducibility of arterial stiffness to that of ABPM for evaluation of its use as a surrogate technique for long-term measurement of vascular health.

MATERIALS AND METHODS

Individuals and inclusion criteria

We analysed IPD from three RCTs investigating the impact of dietary modifications on cardiovascular outcomes. Firstly, the Fruit & Veg study (ISRCTN50011192) tested whether a potassium-rich diet was beneficial for treatment-naive prehypertensive individuals \( (n = 48) \) [8]. Secondly, the MARINA study (ISRCTN66664610, \( n = 312 \)) examined if increasing intake of long-chain n-3 polyunsaturated fatty acids favourably affected endothelial function and arterial stiffness [9]. Finally, the CRESSIDA study (ISRCTN9282106, \( n = 162 \)) considered how following UK dietary guidelines, instead of a traditional British diet, might affect vascular function [10]. All study and trial procedures were performed at Guy’s and St. Thomas’ NHS Foundation Trust. Each study was approved by a local research ethics committee.

Data were eligible for inclusion and analysis if they fulfilled the following criteria: individuals must have had at least two ABPM and two PWV measurements, individual arms of each study did not show a significant change in BP measurements from baseline (statistical method detailed below) and no change in antihypertensive medications during the study. To verify whether individual arms of studies were eligible to be included in this analysis, repeated-measures analysis of variance (ANOVA) was followed by a second baseline measurement approximately 3 weeks later, and then further measurements at 4, 8 and 12 weeks after the second baseline measurement. In Fruit & Veg, the first two measurements were approximately 6 weeks apart, and then subsequent measurements were every 11 weeks. MARINA measured ABPM at baseline, then 6 months and 12 months later. A full schedule of events can be found in Table S1, http://links.lww.com/HJH/C73 (in Supplemental Digital Content). ABPM devices were programmed to take measurements every 30 min from 0700 to 2200 h and hourly between 2200 and 0700 h, but daytime and night-time periods were defined by each participant according to a sleep diary.

PWV was measured by applanation tonometry of the carotid and femoral arteries using the SphygmoCor device (Atcor Medical, Sydney, Australia) after at least 15 min of rest. Further details of study procedures and study outcomes can be found in the published articles [8–10].

Nocturnal dipping

Nocturnal dip category was estimated for each ABPM session firstly according to a simple dichotomous outcome of dipper (night-time SBP fall ≥ 10% of daytime SBP) or nondipper (night-time SBP fall <10% daytime SBP). Dipping status was then further defined according to the four classic dipping patterns (dipper: nocturnal SBP fall >10% of daytime SBP), reduced dipping (nocturnal BP fall 1–10% of daytime SBP), reverse dipping (increase in nocturnal SBP) and extreme dipping (nocturnal SBP fall >20% of daytime SBP) [17].

Data analysis

To verify whether individual arms of studies were eligible to be included in this analysis, repeated-measures analysis of
Effect of regression to the mean (or adaptation to the ABPM device) was analysed using repeated-measures ANOVA in a subset of 199 individuals who had five ABPM measurements. Fleiss' Kappa was calculated to determine agreement above chance in dipping categories.

Statistical tests were performed in SPSS version 25 (IBM, Chicago, USA), and significance defined as a P value less than 0.05. One author (L.K.) had access to all the data and takes responsibility for its integrity and the data analysis.

### RESULTS

**Baseline characteristics**

Participant characteristics at baseline are summarized in Table 1 (n = 501). The cohort was predominantly female (61%), with mean (±SD) age 53.4 ± 8.0 years. Most individuals were of white ethnicity (80%). Mean clinic (seated) SBP and DBP were 124 ± 16 and 80 ± 10 mmHg, respectively. A small proportion of participants in the MARINA trial were on stable antihypertensive medication (4%). No individuals from CRESSIDA or Fruit & Veg were on antihypertensive therapy. Mean baseline PWV was 8.4 ± 1.6 m/s and mean baseline ambulatory SBP was 130 ± 13 mmHg during the day, 110 ± 14 mmHg at night and 125 ± 13 mmHg over 24 h. Mean baseline ambulatory DBP was 79 ± 8 mmHg for day, 65 ± 8 mmHg at night and 76 ± 7 mmHg over 24 h. Mean BMI at baseline was 26.0 ± 3.9 kg/m². There was no significant change in mean BMI over the duration of the studies (P = 0.938).

Baseline SBPday and SBPnight were significantly correlated with age (r = 0.15, P = 0.001 and r = 0.14, P = 0.001 respectively), but DBPday and DBPnight were not

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**TABLE 1. Individual characteristics at baseline**

|                      | CRESSIDA (n = 159) | Fruit & Veg (n = 48) | MARINA (n = 294) | All (n = 501) |
|----------------------|-------------------|----------------------|-----------------|--------------|
| **Age (years)**      | 52.9 ± 8.0        | 45.2 ± 9.4           | 55.1 ± 6.6      | 53.4 ± 8.0   |
| **Female [n (%)]**   | 96 (60)           | 25 (52)              | 184 (63)        | 305 (61)     |
| **Ethnicity**        |                   |                      |                 |              |
| White [n (%)]        | 133 (84)          | 29 (60)              | 239 (81)        | 401 (80)     |
| Black [n (%)]        | 14 (9)            | 10 (21)              | 15 (5)          | 39 (8)       |
| Asian [n (%)]        | 10 (6)            | 9 (19)               | 27 (9)          | 46 (9)       |
| Other/mixed [n (%)]  | 2 (1)             | 0                    | 13 (4)          | 15 (3)       |
| **BMI (kg/m²)**      | 26.0 ± 3.8        | 28.4 ± 3.8           | 25.5 ± 3.9      | 26.0 ± 3.9   |
| **Antihypertensive use [n (%)]** | 0               | 0                    | 11 (4)          | 11 (2)       |
| **PWV (m/s)**        | 7.5 ± 1.2         | 7.9 ± 1.0            | 8.9 ± 1.7       | 8.4 ± 1.6    |
| **Clinic seated measurements:** |                 |                      |                 |              |
| SBP (mmHg)           | 120 ± 16          | 129 ± 12             | 126 ± 16        | 124 ± 16     |
| DBP (mmHg)           | 79 ± 10           | 87 ± 8               | 80 ± 10         | 80 ± 10      |
| HR (bpm)             | 66 ± 9            | 73 ± 9               | 68 ± 9          | 68 ± 9       |
| **Ambulatory measurements:** |               |                      |                 |              |
| SBPday (mmHg)        | 126 ± 13          | 139 ± 14             | 131 ± 13        | 130 ± 13     |
| SBPnight (mmHg)      | 107 ± 14          | 116 ± 14             | 110 ± 13        | 110 ± 14     |
| 24-h SBP (mmHg)      | 122 ± 12          | 135 ± 13             | 126 ± 12        | 125 ± 13     |
| DBPday (mmHg)        | 77 ± 8            | 88 ± 7               | 79 ± 7          | 79 ± 8       |
| DBPnight (mmHg)      | 64 ± 9            | 71 ± 8               | 65 ± 7          | 65 ± 8       |
| 24-h DBP (mmHg)      | 74 ± 7            | 85 ± 7               | 76 ± 7          | 76 ± 7       |
| HRday (bpm)          | 72 ± 9            | 76 ± 7               | 76 ± 8          | 75 ± 8       |
| HRnight (bpm)        | 62 ± 9            | 65 ± 9               | 64 ± 8          | 63 ± 9       |
| 24-h HR (bpm)        | 70 ± 8            | 74 ± 7               | 73 ± 7          | 72 ± 8       |

Values represent means ± standard deviation, or number [percentage].

HR, heart rate; PWV, pulse wave velocity.
(r = 0.02, P = 0.70 and r = 0.85, P = 0.06). Baseline BMI was significantly correlated with all baseline pressure measurements (r = 0.26, P > 0.001 for SBPday, r = 0.29, P < 0.001 for SBPnight, r = 0.16, P < 0.001 for DBPday and r = 0.23, P < 0.001 for DBPnight).

**Associations between blood pressure variability and mean pressures**

Significant associations were observed between mean ambulatory BP values and the variability of those measurements (Fig. 2). For SBP, both day and night measurements demonstrated a significant association between mean values and the SD of those measurements (SBPday r = 0.21, P < 0.001; SBPnight r = 0.27, P < 0.001) (Fig. 2a and c). When the relationship was investigated using the ratio of variability and mean SBP (individual CoV), the strength of the relationship was no longer significant for day measurements (r = 0.03, P = 0.449) and reduced for night (r = 0.15, P = 0.001; Fig. 2b and d).

For ambulatory DBP measurements, a significant positive relationship was observed between mean values and the SD of those measurements (DBPday r = 0.17, P < 0.001 and DBPnight r = 0.29, P < 0.001; Fig. 2e and g). Conducting the analyses with CoV removed the significant association for both DBPday and DBPnight (r = 0.02, P = 0.696 and r = 0.10, P = 0.496, respectively; Fig. 2f and h).

**Within-individual coefficient of variation for repeated ambulatory blood pressure measurements**

Measures of within-individual CoV for each study and for the entire cohort are summarized in Table 2. Qualitative analysis shows that measures of CoV for each BP measurement are similar for each study. In the entire cohort, the CoV for daytime measurements is significantly lower than that compared with night-time measurements: 5.4% (95% CI 5.2–5.6) for SBPday compared with 7.0% (95% CI 6.7–7.3) for SBPnight, and 6.1% (95% CI 5.9–6.4) for DBPday compared with 8.4% (95% CI 8.0–8.7) for DBPnight. CoV is significantly lower for 24-h ABPM measurements: 4.8% (95% CI 4.6–5.0) for SBP, and 5.3% (95% CI 5.1–5.5) for DBP.

Reproducibility of ambulatory measurements was compared between individuals defined as normotensive on their baseline visit compared with those defined as hypertensive (Table 2 and Fig. 3). The mean baseline SBP for the normotensive group was 122 ± 8 mmHg compared with 144 ± 9 mmHg for the hypertensive group. When considering all normotensives versus all hypertensive individuals, there was no clear evidence of any difference in the reproducibility of SBPday, SBPnight, DBPday, or DBPnight. However, both the CRESSIDA and Fruit & Veg studies showed significantly less variability in hypertensive individuals than normotensive individuals for measurements of DBPday: 4.4% (95% CI 3.9–4.9) in hypertensive individuals compared with 5.3% (95% CI 5.0–5.7) in normotensive individuals in CRESSIDA, and 5.5% (95% CI 4.8–6.2) in hypertensive individuals compared with 7.7% (95% CI 6.4–9.1) in normotensive individuals in Fruit & Veg.

**Association of individual risk factors to individual blood pressure variability**

Average estimates of individual BPV, as assessed by the SD, were as follows: SBPday SD 6.1 ± 3.3 mmHg, SBPnight SD 6.6 ± 3.8 mmHg, DBPday SD 4.1 ± 2.3 mmHg and DBPnight SD 4.4 ± 2.5 mmHg. BPV was not correlated with age for SBPday SD, SBPnight SD, DBPday SD, DBPnight SD (all P > 0.05). BMI at baseline was significantly correlated with SBPday SD (r = 0.09, P = 0.04), SBPnight SD (r = 0.20, P < 0.001) and DBPnight SD (r = 0.19, P < 0.001), and had a borderline significant correlation with DBPday SD (r = 0.09, P = 0.054).

Table 3 summarizes multivariable linear regression investigating the associations between BPV to individual demographics and mean BP. No significant associations were demonstrated for age, sex or PWV with SD for SBPday, SBPnight, DBPday or DBPnight. SBPday SD was independently associated with nonwhite ethnicity, use of antihypertensive medication and mean SBPday. SBPnight SD was independently associated with baseline BMI and mean SBPnight-DBPnight SD was only associated with mean DBPnight SD. DBPnight SD was independently associated with baseline BMI and mean DBPnight. Further analyses were performed examining the effect of mean sleep duration on night-time variability, in a subset of 207 individuals in whom these data were available (the CRESSIDA and Fruit & Veg participants). Mean sleep duration was not independently associated with SBPnight SD (P = 0.482) or DBPnight SD (P = 0.160), as shown in Supplemental Digital Content, Table S3, http://links.lww.com/HJH/C73, which details the full linear regression models.

**Adaptation to the ambulatory blood pressure monitoring device**

Adaptation to the ABPM device was tested in a subset of 199 individuals who had the full five measures of each BP. Repeated-measures ANOVA shows no evidence of adaptation to the device in terms of SBPday, SBPnight or DBPday (all P > 0.05). However, DBPnight changed significantly over the course of sequential measurements, being at its lowest on the baseline visit, highest on second assessment, then decreasing sequentially (P = 0.001).

**Variability of arterial stiffness measurements**

Baseline PWV was 8.4 ± 1.6 m/s, compared with 8.3 ± 1.6 m/s at study endpoint (P = 0.016). Mean PWV was positively correlated with mean ABPM values: SBPday (r = 0.40, P < 0.001), SBPnight (r = 0.41, P < 0.001), DBPday (r = 0.25, P < 0.001) and DBPnight (r = 0.30, P < 0.001). Reproducibility of PWV measurements differed between studies (Table 2). There was a significantly lower CoV for PWV measured in the CRESSIDA study: 7.6% (95% CI 6.7–8.4) compared with the Fruit & Veg and MARINA studies: 10.4% (95% CI 9.3–11.5) and 12.1% (95% CI 11.1–13.1), respectively. In the total cohort, CoV of repeated PWV measurements was 10.7% (95% CI 9.0–10.9), with no statistical difference demonstrated between the PWV reproducibility between normotensive and hypertensive individuals: 10.2% (95% CI 9.4–10.9) versus 11.5% (95% CI 10.5–12.6).
The mean PWV and its SD were significantly and positively correlated ($r = 0.28$, $P < 0.001$). However, there were no significant correlations between mean PWV and BPV of $SBP_{day}$, $SBP_{night}$, $DBP_{day}$ or $DBP_{night}$.

Variability of heart rate measurements
Baseline HR measured in clinic was $68 \pm 9$, compared with $75 \pm 7$ for the baseline HR measured by ABPM ($P < 0.001$). CoV of HR measurements was $6.3\%$ (95% CI 6.1–6.5).

FIGURE 2 Associations between individual ambulatory mean pressures and SD or coefficient of variation. (a) Daytime systolic SD. (b) Daytime systolic CoV. (c) Night-time systolic SD. (d) Night-time systolic CoV. (e) Daytime diastolic SD. (f) Daytime diastolic CoV. (g) Night-time diastolic SD. (h) Night-time diastolic CoV. CoV, coefficient of variation; SD, standard deviation.
and hypertensive individuals ($\kappa = 0.132$, $P < 0.001$ and $\kappa = 0.187$, $P < 0.001$, respectively) when analysed over five ABPM measurements ($n = 194$).

Using the four categories of dipping (reverse, reduced, normal and extreme), the majority of normotensive and hypertensive individuals were again classed as normal dippers (51 and 44%, respectively). Both groups also showed a tendency to change category over the course of their measurements. In the normotensive group, 271 (84%) changed their dipping category, and in the hypertensive group, 141 (80%) changed their dipping category. In individuals with the full five measurements, only 11% of normotensive individuals maintained their original dipping category ($\kappa = 0.107$, $P < 0.001$). Similarly, only 11% of hypertensive individuals maintained their original dipping category over five ABPM measurements ($\kappa = 0.160$, $P < 0.001$).

**DISCUSSION**

To our knowledge, this is the largest study to examine reproducibility of serial ABPM measurements in a cohort of adults with minimal cardiovascular comorbidities. Reproducibility estimates are not dissimilar to those calculated by others. Our CoV estimates of 5.4 and 6.1% for daytime SBP

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**Table 2. Measures of reproducibility in ambulatory blood pressure and pulse wave velocity**

|                      | CRESSIDA | Fruit & Veg | MARINA | ALL         |
|----------------------|----------|-------------|--------|-------------|
|                      | $n$      | CoV, % (95% CI) | $n$      | CoV, % (95% CI) | $n$      | CoV, % (95% CI) | $n$      | CoV, % (95% CI) |
| All individuals      | 159      | 5.0 (4.8–5.4) | 48      | 5.4 (4.9–6.0) | 294      | 5.6 (5.3–5.9) | 501      | 5.4 (5.2–5.6) |
| SBP$_{ sys }$        |          |             |         |             |          |             |          |             |
| hypertensive         |          |             |         |             |          |             |          |             |
| SBP$_{ sys }$        | 6.7 (6.3–7.0) | 7.5 (6.7–8.4) | 7.1 (6.7–7.5) | 7.0 (6.7–7.3) | 9.0 (8.5–9.5) | 8.1 (7.2–8.9) | 8.0 (7.5–8.5) | 8.4 (8.0–8.7) |
| hypertensive         | 5.1 (4.8–5.4) | 6.3 (5.7–7.0) | 6.6 (6.2–7.0) | 6.1 (5.9–6.4) | 5.9 (5.1–5.8) | 5.5 (5.1–5.8) | 6.3 (6.0–6.8) | 6.3 (6.0–6.5) |
| hypertensive         | 5.8 (5.5–6.1) | 6.0 (5.3–6.6) | 5.9 (5.6–6.3) | 5.9 (5.7–6.1) | 7.6 (6.7–8.4) | 10.4 (9.3–11.5) | 12.1 (11.1–13.1) | 10.7 (9.0–10.9) |
| Nocturnal dipping    |          |             |         |             |          |             |          |             |
| hypertensive         |          |             |         |             |          |             |          |             |
| hypertensive         | 5.3 (4.9–5.6) | 6.0 (5.0–7.0) | 5.6 (5.2–6.0) | 5.5 (5.2–5.8) | 6.7 (6.2–7.1) | 7.2 (5.9–8.5) | 7.0 (6.5–7.5) | 6.9 (6.6–7.2) |
| hypertensive         | 4.8 (4.5–5.1) | 4.8 (3.9–5.6) | 4.7 (4.3–5.1) | 4.7 (4.5–5.0) | 5.3 (5.0–5.7) | 7.7 (6.4–9.1) | 6.4 (5.9–6.8) | 6.1 (5.8–6.4) |
| hypertensive         | 9.2 (8.6–9.8) | 7.7 (6.3–9.1) | 8.3 (7.7–8.9) | 8.6 (8.2–9.0) | 5.0 (4.6–5.3) | 6.5 (5.3–7.6) | 5.3 (4.9–5.7) | 5.3 (5.0–5.5) |
| hypertensive         | 6.1 (5.7–6.5) | 6.5 (5.4–7.6) | 6.3 (5.9–6.8) | 6.3 (6.0–6.6) | 7.4 (6.9–7.8) | 7.0 (5.7–8.3) | 8.7 (8.0–9.4) | 8.1 (7.7–8.5) |
| hypertensive         | 6.0 (5.6–6.3) | 5.4 (4.4–6.4) | 5.8 (5.4–6.3) | 5.9 (5.6–6.1) | 7.1 (6.2–8.0) | 11.0 (9.1–13.0) | 11.7 (10.5–13.0) | 10.2 (9.4–10.9) |
| PWV                   |          |             |         |             |          |             |          |             |
| hypertensive         |          |             |         |             |          |             |          |             |
| hypertensive         | 4.4 (3.9–4.9) | 5.1 (4.4–5.7) | 5.6 (5.1–6.2) | 5.3 (4.9–5.6) | 6.6 (5.8–7.4) | 7.8 (6.7–8.8) | 7.3 (6.5–8.0) | 7.2 (6.7–7.7) |
| hypertensive         | 4.1 (3.6–4.6) | 5.0 (4.4–5.7) | 5.1 (4.6–5.6) | 4.9 (4.5–5.2) | 4.4 (3.9–4.9) | 5.5 (4.8–6.2) | 6.9 (6.2–7.6) | 6.2 (5.8–6.6) |
| hypertensive         | 8.2 (7.3–9.2) | 8.3 (7.2–9.4) | 7.6 (6.8–8.3) | 7.8 (7.3–8.4) | 4.1 (3.6–4.6) | 5.3 (4.6–6.0) | 5.6 (5.1–6.2) | 5.3 (4.9–5.6) |
| hypertensive         | 6.9 (6.1–7.7) | 8.3 (7.2–9.3) | 7.6 (6.8–8.4) | 7.6 (7.1–8.1) | 5.3 (4.7–5.9) | 6.2 (5.4–7.1) | 6.1 (5.5–6.7) | 5.9 (5.6–6.3) |
| hypertensive         | 9.0 (6.9–11.1) | 10.0 (8.7–11.4) | 12.7 (10.9–14.5) | 11.5 (10.5–12.6) | 135 mmHg. Hypertension defined as baseline ambulatory SBP$_{ day }$ < 135 mmHg.
and DBP, respectively, are close to the 5.5 and 4.9% calculated by Warren et al. [20] in a cohort of 163 individuals of similar age (although with a higher proportion of antihypertensive use) and lower than 7.4 and 6.3% calculated by Mansoor et al. [3] in their cohort of hypertensive patients (n = 25). Our nighttime CoVs were slightly higher than those obtained by Mansoor et al. [3]: 7.0% compared with 6.3% for night-time SBP, and 8.4% compared with their 7.1% for night-time DBP [3]. Despite the large difference in baseline SBPday between the normotensive and hypertensive group, we did not demonstrate any marked differences in ABPM measurement reproducibility in normotensive versus hypertensive individuals. By using CoV as a measure of reproducibility (rather than SD, which is correlated to mean BP), we show that in our cohort, ABPM measurements were no more variable in stable hypertensive individuals than in normotensive individuals when the mean BP was accounted for.

Variability of our night-time measurements generally exceeded that of daytime measurements, as also found by Bo et al. [21]. This could be attributable to inconsistency of nocturnal dipping patterns [22] or direct interruption of sleep due to the operation of the ABPM device. Poor sleep quality is associated with increased BPV [23] and with increased BP [24], but it is contentious whether ABPM devices impair sleep quality enough to produce a significant increase in nocturnal pressures [25,26]. We were not able to analyse the effect of sleep quality in this study, but sleep duration did not appear to have a significant effect on night-time variability. When we analysed patterns of nocturnal dipping, we found little agreement above chance in

| TABLE 3. Multivariable linear regression showing associations between variability of ambulatory blood pressures to mean blood pressure and demographic risk factors |
|-----------------------------------------------|
|                     | SBP_{day} SD |                     | SBP_{night} SD |                     | DBP_{day} SD |                     | DBP_{night} SD |
|----------------------|--------------|---------------------|---------------|---------------------|--------------|---------------------|----------------|
| Age (years)          | 0.030        | 0.578               | 0.020         | 0.705               | -0.062       | 0.256               | 0.088          | 0.094          |
| Sex (male/female)    | 0.030        | 0.521               | -0.042        | 0.349               | 0.040        | 0.397               | 0.014          | 0.763          |
| Ethnicity (white/other) | 0.090       | 0.049               | 0.023         | 0.608               | 0.029        | 0.542               | 0.059          | 0.838          |
| BMI (kg/m²)          | 0.027        | 0.561               | 0.097         | 0.033               | 0.052        | 0.277               | 0.136          | 0.003          |
| PWV (m/s)            | -0.056       | 0.319               | -0.092        | 0.088               | -0.019       | 0.733               | -0.106         | 0.055          |
| Antihypertensives (yes/no) | 0.112      | 0.012               | -0.049        | 0.251               | 0.083        | 0.068               | 0.034          | 0.437          |
| Mean SBP_{day} (mmHg) | 0.271       | 0.001               | -            | -                   | 0.023        | 0.709               | -              | -              |
| Mean DBP_{day} (mmHg) | -0.079      | 0.279               | -            | -                   | 0.155        | 0.008               | -              | -              |
| Mean SBP_{night} (mmHg) | -          | -                   | 0.414        | <0.001              | -            | -                   | 0.063          | 0.456          |
| Mean DBP_{night} (mmHg) | -          | -                   | -0.093       | 0.245               | -            | -                   | 0.223          | 0.006          |

B, standardized regression coefficient. PWV, pulse wave velocity; SD, standard deviation (measure of blood pressure variability). \( P < 0.05 \) highlighted in bold.
categorisation of dipping status. This trend persisted whether we used four categories of classification, or a simplified dichotomous classification, and with little difference seen between normotensive and hypertensive individual groups. Although abnormal nocturnal dipping has been shown to be associated with adverse cardiovascular outcomes [27], its poor reproducibility shown by ourselves and others [21,22,28] may limit its use for stratifying risk. As many studies on nocturnal dip variability examine only two measurements, further large studies are needed to examine reproducibility of nocturnal dip over multiple measurements with an emphasis on determining subgroups particularly prone to high variation.

We have shown that BPV, an important predictor of cardiovascular risk, is positively associated with mean BP but were unable to demonstrate any significant associations with age, sex or concurrent arterial stiffness when the mean BP was accounted for. Arterial stiffening may be a long-term consequence rather than a cause of BPV [15], hence the lack of association seen in cross-sectional regression. Increased BMI was associated with a higher baseline BP and increased variability of night-time measurements, but not daytime pressures, which may reflect findings by others that higher BMI is associated with increased BPV, and disruption of normal nocturnal dipping patterns [29,30]. White participants appeared to have less variability in their SBPday measurements compared with nonwhite ethnicity individuals, in agreement with other studies showing that African–Americans have higher BPV than white individuals, as well as higher mean ambulatory pressures [31], for which several physical and socioeconomic reasons have been suggested [32].

A secondary aim of this study was to examine if the variability of arterial stiffness, as measured by PWV, was superior to that of ABPM. Overall, PWV was found to have a CoV of 10.7% for the whole cohort, which is similar to that found by others in short-term studies [33], but higher than the CoV for the BP measures, which ranged from 5.4 to 8.4%. Coupled with the fact that PWV requires specialist equipment and user training, this suggests that, unless it is more strongly related to risk of clinical outcomes, it is not preferable as a surrogate measurement for long-term BP monitoring. PWV measurements appeared more variable in hypertensive compared with normotensive individuals, but this is to be expected given that mean and SD values of PWV were correlated, and PWV is itself highly correlated with concurrent BP.

Use of ABPM is becoming more widespread, as current guidelines recommend its use to confirm a new diagnosis of hypertension [34,35]. However, for long-term monitoring of BP, NICE still advises use of clinic BP measurement, with ABPM suggested as a confirmatory tool for individuals who could have white-coat or masked hypertension [35]. Reproducibility of repeated ABPM has been studied, but often in small cohorts and a wide range of reproducibility indices used across the literature. Our cohort was composed of individuals with minimal cardiovascular morbidities and who did not require initiation or alteration of antihypertensive medication during the study period. In such individuals, it could be hypothesized that variability of BP measurements should be minimal. However, we have shown that the within-individual variability of ABPM measurements is still large when considered in clinical context. A borderline hypertensive clinic individual may be given ABPM to confirm or refute the presence of true hypertension. If their true daytime SBP was 140 mmHg, however, a CoV of 5.4% for SBPday by ABPM implies that 95% of readings will normally occur within a range of 125–155 mmHg, making diagnosis uncertain. Similarly, for a true daytime diastolic pressure of 90 mmHg, 95% of measurements would occur within a range of 78–102 mmHg (based on a CoV of 6.1%). Night-time estimates may be subject to even greater variability, as we have noted that the CoV of night-time measurements is significantly higher than those found during the day. Currently, NICE only recommends use of daytime ABPM to guide diagnosis [35], but future work could explore the use of night-time and 24-h BP to guide antihypertensive therapy, as nocturnal BP is correlated with cardiovascular outcomes [36,37], and variability of 24-h BP is less than daytime BP, as shown in this work and others [4,38–40].

Clinicians should note that SD of measurements is proportional to mean pressure and precise assessment of BP in a hypertensive individual may therefore be subject to additional complexity. An additional consideration in the use of single ABPM measurements to guide treatment is the possibility of an adaptive response to the device, whereby the first use elicits an additional pressor response with subsequent values showing regression to the mean. Although we were unable to show evidence of adaptation in terms of SBPday, SBPnight or DBPnight, we did note some changes in DBPnight over the course of sequential measurements and nocturnal ABPs have been shown to be susceptible to adaptation as well as daytime measurements [38,41].

Our recent work using Monte Carlo simulations of BP treatments showed that measurement error is the main cause for misclassification of BP target when undertaking stepwise titration of antihypertensive therapy [16,42]. Readings of low error are likely to improve BP control, a conclusion supported by general consensus [43,44]. It is interesting to note that the measurement margins calculated here are in excess of the likely response to antihypertensive monotherapy (~ 9.1 mmHg SBP, ~ 5.5 mmHg DBP), and may even exceed that expected for dual therapy in some instances [45], highlighting the limitations of single ABPM measurements.

Limitations
The present study is subject to several important limitations. Firstly, this study uses retrospective data from intervention-al studies, which were designed to detect differences from baseline in ABPM and PWV, rather than assess variability within a stable population over time. Furthermore, the three studies differ in design and so the extent to which their data are directly comparable must be considered. The analyses presented here were designed to mitigate against these potential issues. Firstly, each study arm was only included if there was no significant change in measurements from baseline. This is a different approach to that used within each study, which generally compared intervention. In the CRESSIDA study this showed a significant 4.2 mmHg reduction in ambulatory daytime SBP in the intervention compared to control group. Our approach was defined a priori and was designed to maximise the data available, albeit with a recognition that various interventions may
have an unknown impact on measures of interest. For example, we note that subsequent analysis from the MARINA study has identified that genotype may have dictated an individual's response to the fish oils given [46]. However, even with a potential postintervention increase up to 5 mmHg on endpoint SBP, our CoV estimates for SBP would not be significantly altered (calculation not shown). Secondly, we used IPD rather than summary data to provide more reliable results [47]. Thirdly, the limited number of repeat measurements for each participant may have inflated true values for individual variability but does approximate better to clinical practice than a high number of repeated ABPMs. The consistency of results between the three different studies provides some reassurance for our approach and the comparability of the datasets.

In conclusion, this study highlights that although ABPM is the gold standard for BP measurement and monitoring, variability between measurements may result in misclassification and incorrect treatment decisions. Within our analysis population, PWV measurement was not a more reproducible technique than ABPM when assessed as a CoV. Repeated ABPM may be necessary to refine antihypertensive therapy.

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Data supporting this article are not openly available due to ethical restrictions. A descriptive record can be found in the Kings College London research data repository at https://doi.org/10.18742/20348892. Data may be shared on reasonable request by application to Professor Tom Sanders, tom.sanders@kcl.ac.uk.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Constanti M, Boffa R, Floyd CN, Wierzbicki AS, McManus RJ, Glover M. Options for the diagnosis of high blood pressure in primary care: a systematic review and economic model. J Hum Hypertens 2021; 35:455–461.
2. James GD, Pickering TG, Yee LS, Harshfield GA, Riva S, Laragh JH. The reproducibility of average ambulatory, home, and clinic pressures. Hypertension 1988; 11:545–549.
3. Mansoor G, McCabe E, White W. Long-term reproducibility of ambulatory blood pressure. J Hypertens 1994; 12:703–708.
4. Palatini P, Morimino P, Canali C, Santonastaso M, De Venuto G, Zanata G, et al. Factors affecting ambulatory blood pressure reproducibility: results of the HARVEST trial. Hypertension 1994; 23:211–216.
5. Boffa RJ, Constanti M, Floyd CN, Wierzbicki AS. Hypertension in adults: summary of updated NICE guidance. BMJ 2019; 367:1–6.
6. Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. Hypertension 2002; 39:795–796
7. Guisepppe M, Guido G, Guido P, Luisa G, Giovanni B, Gianfranco P, et al. Effects of blood-pressure measurement by the doctor on patient’s blood pressure and heart rate. Lancet 1985; 2:695–698.
8. Berry SE, Mulla UZ, Chowienczyk PJ, Sanders TAB. Increased potassium intake from fruit and vegetables or supplements does not lower blood pressure or improve vascular function in UK men and women with early hypertension: a randomised controlled trial. Br J Nutr 2010; 104:1839–1847.
9. Sanders TAB, Hall WL, Maniou Z, Lewis F, Seed PT, Chowienczyk PJ. Effect of low doses of long-chain n-3 PUFAs on endothelial function and arterial stiffness: a randomized controlled trial. Am J Clin Nutr 2011; 94:975–980.
10. Reidlinger DP, Darzi J, Hall WL, Seed PT, Chowienczyk PJ, Sanders TAB, et al. How effective are current dietary guidelines for cardiovascular disease prevention in healthy middle-aged and older men and women? A randomized controlled trial. Am J Clin Nutr 2015; 101:922–930.
11. Rothwell PM, Howard SC, Dolan E, O’Brien E, Dobson JE, Dahlo¨f B, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 2010; 375:895–905.
12. Diaz KM, Tanner RM, Falzon L, Levitan EB, Reynolds K, Shimbo D, et al. Visit-to-visit variability of blood pressure and cardiovascular disease and all-cause mortality: a systematic review and meta-analysis. Hypertension 2014; 64:965–982.
13. Stevens SL, Wood S, Koshtiari C, Law K, Glasziou P, Stevens RJ, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. BMJ 2016; 354:i14–i16.
14. Li W, Yu Y, Liang D, Jia EZ. Factors associated with blood pressure variability based on ambulatory blood pressure monitoring in subjects with hypertension in China. Kidney Blood Press Res 2017; 42:267–275.
15. Zhou TL, Henry RMA, Stehouwer CDA, Van Sloten TT, Reesink KD, Koom AA. Blood pressure variability, arterial stiffness, and arterial remodeling the Maastricht study. Hypertension 2018; 72:1002–1010.
16. Zantis I, Floyd CN, Barrett JE, Bunce F, Frohimaier C, Shunkar F, et al. Monte Carlo simulation of uncertainty to identify barriers to optimizing blood pressure control. J Hypertens 2020; 38:2518–2524.
17. O’Brien E, Parati G, Sergusoa G, Asmar R, Beilin L, Bilo G, et al. European society of hypertension position paper on ambulatory blood pressure monitoring. J Hypertens 2013; 31:1731–1768.
18. Bland JM, Altman DG. Measurement error proportional to the mean. Br Med J 1996; 313:106.
19. Bland M. How should I calculate a within-subject coefficient of variation? 2006. https://www-users.york.ac.uk/~mb58/means/cv.htm (Accessed 27 May 2022).
20. Warren RE, Marshall T, Padfield PL, Chubushik S. Variability of office, 24-h ambulatory, and self-monitored blood pressure measurements. Br J Gen Pract 2010; 60:675–680.
21. Bo Y, Kwok KO, Chung VCH, Yu CP, Tsoi KKF, Wong SYS, et al. Short-term reproducibility of ambulatory blood pressure measurements: a systematic review and meta-analysis of 35 observational studies. J Hypertens 2020; 38:2095–2109.
22. Cuspidi C, Meani S, Salerno M, Valerio C, Fusi V, Severgnini B, et al. Reproducibility of nocturnal blood pressure fall in early phases of untreated essential hypertension: a prospective observational study. J Hum Hypertens 2004; 18:503–509.
23. Liu X, Yan G, Bullock I, Barlesdale DJ, Logan JG. Sleep moderates the association between arterial stiffness and 24-h blood pressure variability. Sleep Med 2021; 83:222–229.
24. Oume M, Obayashi K, Asai Y, Ogura M, Takeuchi K, Tai Y, et al. Objective sleep quality and night-time blood pressure in the general elderly population: a cross-sectional study of the HEIJO-KYO cohort. J Hypertens 2018; 36:601–607.
25. Schwab A, Eriksson G. Effect on sleep but not on blood pressure of nocturnal noninvasive blood pressure monitoring. J Hypertens 1992; 10:189–194.
26. Petersen EH, Theilade S, Hansen TW, Lindhardt MK, Rossing P. Cuff inflations do not affect night-time blood pressure: comparison of 24-h ambulatory blood pressure measured by a cuff and a tonometric device in type 2 diabetes. Blood Press Monit 2015; 20:369–372.
27. Fagard RH, Thijs L, Staessen JA, Clement DL, De Buyzere ML, De Bacquer DA. Night-day blood pressure ratio and dipping pattern as predictors of death and cardiovascular events in hypertension. J Hum Hypertens 2009; 23:645–653.

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28. Burgos-Alonso N, Ruiz Arzalluz MV, García-Alvarez A, Fernandez-Fernandez de Quincoces D, Grandes G. Reproducibility study of nocturnal blood pressure dipping in patients with high cardiovascular risk. J Clin Hypertens 2021; 23:1041–1050.

29. Chen H, Zhang R, Zheng Q, Yan X, Wu S, Chen Y. Impact of body mass index on long-term blood pressure variability: a cross-sectional study in a cohort of Chinese adults. BMC Public Health 2018; 18:1193.

30. Kotsis V, Stabouli S, Bouldin M, Low A, Tsamandidis S, Zakopoulos N. Impact of obesity on 24-hour ambulatory blood pressure and hypertension. Hypertension 2005; 45:602–607.

31. Li Z, Snieder H, Su S, Harshfield GA, Treiber FA, Wang X. A longitudinal study of blood pressure variability in African-American and European American youth. J Hypertens 2010, 28:715–722.

32. Muntner P, Lewis CE, Diaz KM, Carson AP, Kim Y, Calhoun D, et al. Racial differences in abnormal ambulatory blood pressure monitoring measures: results from the coronary artery risk development in young adults (CARDIA) study. Am J Hypertens 2015; 28:640–648.

33. Grillo A, Parati G, Rovina M, Moretti F, Salvi L, Gao L, et al. Short-term repeatability of noninvasive aortic pulse wave velocity assessment: comparison between methods and devices. Am J Hypertens 2018; 31:80–88.

34. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018; 39:3021–3104.

35. National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management. 2019. https://www.nice.org.uk/guidance/ng136.

36. Roush GC, Fagard RH, Salles GF, Pierdomenico SD, Reboldi G, Verdecchia P, et al. Prognostic impact from clinic, daytime, and nighttime systolic blood pressure in nine cohorts of 13844 patients with hypertension. J Hypertens 2014; 32:2352–2360.

37. Cardoso CRL, Salles GF. Associations of the nocturnal blood pressure fall and morning surge with cardiovascular events and mortality in individuals with resistant hypertension. J Hypertens 2021; 39:1177–1187.

38. Musso NR, Vergassola C, Barone C, Lotti G. Ambulatory blood pressure monitoring: how reproducible is it? Am J Hypertens 1997; 10:936–939.

39. Stergiou GS, Hailas NM, Gantzjarou AP, Skeva II, Kalkana CB, Boussias LG, et al. Reproducibility of home, ambulatory, and clinic blood pressure: implications for the design of trials for the assessment of antihypertensive drug efficacy. Am J Hypertens 2002; 15:101–104.

40. Campbell P, Ghiuman N, Wakefield D, Wolfson L, White WR. Long-term reproducibility of ambulatory blood pressure is superior to office blood pressure in the very elderly. J Hum Hypertens 2010; 24:749–754.

41. Moore MN, Atkins FR, Alissay ML, Hare JL, Marwick TH, et al. Regression to the mean of repeated ambulatory blood pressure monitoring in five studies. J Hypertens 2019; 37:24–29.

42. Augustin A, Coutts L, Zanisi L, Wierzbicki AS, Shankar F, Chowienczyk PJ, et al. Impact of therapeutic inertia on long-term blood pressure control: a Monte Carlo simulation study. Hypertension 2021; 77:1350–1359.

43. Muntner P, Shimbo D, Carey RM, Charleston JB, Gaillard T, Misra S, et al. Measurement of blood pressure in humans: a scientific statement from the American Heart Association. Hypertension 2019; 73:E35–E66.

44. Stergiou GS, Parati G, Vlachopoulos C, Achimastos A, Andreadis E, Asmar R, et al. Methodology and technology for peripheral and central blood pressure and blood pressure variability measurement: current status and future directions - Position statement of the European Society of Hypertension Working Group on blood pressure monitoring a. J Hypertens 2016; 34:1665–1677.

45. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. Br Med J 2005; 326:1427–1431.

46. AlSaleh A, Maniou Z, Lewis FJ, Hall WL, Sanders TAB, O’Dell SD. Interaction between a CSK gene variant and fish oil intake influences blood pressure in healthy adults. J Nutr 2014; 144:267–272.

47. Tierney JF, Vale C, Riley R, Smith CT, Stewart L, Clarke M, et al. Individual participant data (IPD) meta-analyses of randomised controlled trials: guidance on their use. PLoS Med 2015; 12:1–16.