# Is Isolated Nocturnal Hypertension A Reproducible Phenotype?

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**BACKGROUND**
Isolated nocturnal hypertension (INH), defined as nocturnal without daytime hypertension on ambulatory blood pressure (BP) monitoring (ABPM), has been observed to be associated with an increased risk of cardiovascular disease (CVD) events and mortality. The aim of this study was to determine the short-term reproducibility of INH.

**METHODS**
The Improving the Detection of Hypertension Study enrolled a community-based sample of adults ($N$ = 282) in upper Manhattan without CVD, renal failure, or treated hypertension. Each participant completed two 24-hour ABPM recordings (ABPM1: first recording and ABPM2: second recording) with a mean ± SD time interval of 33 ± 17 days between recordings. Daytime hypertension was defined as mean awake systolic/diastolic BP ≥ 135/85 mm Hg; nocturnal hypertension as mean sleep systolic/diastolic BP ≥ 120/70 mm Hg; INH as nocturnal without daytime hypertension; isolated daytime hypertension (IDH) as daytime without nocturnal hypertension; day and night hypertension (DNH) as daytime and nocturnal hypertension, and any ambulatory hypertension as having daytime and/or nocturnal hypertension.

**RESULTS**
On ABPM1, 26 (9.2%), 21 (7.4%), and 50 (17.7%) participants had INH, IDH, and DNH, respectively. On ABPM2, 24 (8.5%), 19 (6.7%), and 54 (19.1%) had INH, IDH, and DNH, respectively. The kappa statistics were 0.21 (95% confidence interval (CI) 0.04–0.38), 0.25 (95% CI 0.06–0.44), and 0.65 (95% CI 0.53–0.77) for INH, IDH, and DNH respectively; and 0.72 (95% CI 0.63–0.81) for having any ambulatory hypertension.

**CONCLUSIONS**
Our results suggest that INH and IDH are poorly reproducible phenotypes, and that ABPM should be primarily used to identify individuals with daytime hypertension and/or nocturnal hypertension.

*Keywords* : ambulatory blood pressure; isolated nocturnal hypertension; reproducibility.

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Ambulatory blood pressure (BP) monitoring (ABPM) complements clinic BP (CBP) by its ability to quantify out-of-office BP. Several distinct BP phenotypes can be determined by ABPM that cannot be determined by CBP[1] including the presence of nocturnal hypertension. In the general population, the prevalence of nocturnal hypertension is approximately 30–45%.[2,3] Prior studies suggest that nocturnal hypertension is associated with an increased risk of cardiovascular disease (CVD) events and mortality.[2,4]

More recently, a specific subtype of nocturnal hypertension, isolated nocturnal hypertension (INH), defined as nocturnal hypertension without daytime hypertension on ABPM, has been investigated as a CVD risk factor.[3,5,6] It has been reported that individuals with INH may have an increased risk of CVD events and mortality when compared with individuals with daytime and nocturnal normotension

(DNN).[3,5,6] Currently, INH can only be identified using ABPM because its diagnosis requires the measurement of nighttime BP, and most individuals with INH have non-elevated CBP.[3] The confluence of increased CVD events and mortality risk, and a failure to be diagnosed by conventional clinic BP measurement, makes INH a potentially important ABPM phenotype.

Prior studies have shown that nocturnal hypertension has good short-term reproducibility.[7,8] However, scarce data exist on the short-term reproducibility of INH. The reproducibility of INH has implications as to whether a single ABPM recording period can be used to identify this phenotype. The aim of this study was to determine the short-term reproducibility of INH on 24-hour ABPM among individuals not taking antihypertensive medications.

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## METHODS

### Sample population

The Improving the Detection of Hypertension Study is an ongoing community-based study of adults in upper Manhattan designed to compare the effectiveness of different strategies for diagnosing ambulatory hypertension. Participants were recruited from the upper Manhattan community surrounding Columbia University Medical Center. Participants were ineligible for the study if they had any of the following: screening systolic CBP ≥ 160 mm Hg or diastolic CBP ≥ 105 mm Hg; evidence of secondary hypertension; or were taking antihypertensive medications or other medications that are known to affect BP (i.e., steroids, tricyclic antidepressants, etc). Participants were also excluded if they had a history of overt CVD, chronic kidney disease, liver disease, adrenal disease, thyroid disease, rheumatologic disease, hematologic disease, organ transplantation, cancer, dementia, or were pregnant. The study protocol was approved by the Institutional Review Board at Columbia University and all participants provided informed consent.

### Study procedures

Information about demographics and CVD risk factors were ascertained in all enrolled participants. At the first visit, participants rested in the seated position for at least 5 minutes, after which 3 CBP readings (with at least 1-minute intervals between readings) were performed by a research nurse/technician using a sphygmomanometer (Baum, Copiague, NY) with an appropriate-sized arm cuff and stethoscope. Twenty-four-hour ABPM was performed twice for each participant with the first ABPM recording period (ABPM1) occurring immediately after the first visit. The second ABPM recording period (ABPM2) occurred at a mean ± SD of 33 ± 17 days after the first recording period. Prior to each ABPM measurement period, participants were fitted with an appropriate-sized ABPM (Spacelabs Model 90207; Snoqualmie, WA) arm cuff and a wrist actigraphy device (ActiWatch; Phillips Respironics, Murrayville, PA). Both devices were returned the next day at the conclusion of the 24-hour monitoring period. For each ABPM recording periods, BP measurements were taken at 30-minute intervals throughout the 24-hour period. In the literature, the terms "nighttime" and "daytime" are often used interchangeably with "sleep" and "awake," respectively.[9] In the current study, the nighttime and daytime periods were defined by the onset of sleep and awake periods, assessed using the wrist actigraphy device supplemented by participant diary reports. Editing criteria for ABPM readings are described in the Supplementary Methods online.

Two-dimensional echocardiograms were performed and left ventricular (LV) measurements were obtained according to the recommendations of the American Society of Echocardiography.[10] LV mass (LVM, g) was calculated using the American Society of Echocardiography formula.[10] LVM index (LVMI g/m²) was calculated by dividing LVM by estimated body surface area. LV hypertrophy (LVH) was defined as LVMI ≥ 89 g/m² in females and ≥ 103 g/m² in males.[10]

### Definitions of hypertension categories

Clinic hypertension was defined as a mean systolic CBP ≥ 140 mm Hg or mean diastolic CBP ≥ 90 mm Hg using the 3 CBP readings from the first visit. For each ABPM recording period, nocturnal hypertension was defined as mean sleep systolic BP ≥ 120 mm Hg or mean diastolic BP ≥ 70 mm Hg.[9] Daytime hypertension was defined as mean awake systolic BP ≥ 135 mm Hg or mean awake diastolic BP ≥ 85 mm Hg.[9] INH was defined as nocturnal without daytime hypertension, isolated daytime hypertension (IDH) as daytime without nocturnal hypertension, day and night hypertension (DNH) as daytime and nocturnal hypertension, and day and night normotension (DNN) as the absence of both daytime and nocturnal hypertension. Any ambulatory hypertension was defined as having daytime and/or nocturnal hypertension. This latter group includes INH, IDH, and DNH. Analyses were performed in which nocturnal hypertension, daytime hypertension, any ambulatory hypertension, INH, IDH, DNH, and DNN were defined by using systolic BP only and repeated using diastolic BP only, as defined in the Supplementary Methods. BP dipping ratio was calculated as mean sleep to awake systolic BP. Non-dipping status was defined as BP dipping ratio >0.90.[9,11]

Masked hypertension is defined as the absence of clinic hypertension but with ambulatory hypertension. In this study, individuals without clinic hypertension ($N = 246$) who had nocturnal hypertension were considered to have masked nocturnal hypertension. Among those without clinic hypertension, analogous definitions were used to define masked daytime hypertension, any masked ambulatory hypertension, masked INH, masked IDH, masked DNH, and DNN without clinic hypertension, respectively.

### Statistical analyses

Of the 375 participants, who were enrolled between March 2011 and October 2013, 85 did not have ≥80% of the planned ABPM readings at ABPM1 and ABPM2, leaving a sample size of 290 participants. Of the 290 participants, using the ABPM validity criteria used in the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO),[12] another 8 participants did not have 10 or more readings for awake BP and/or did not have 5 or more readings for sleep BP, leaving a final sample size of 282 participants. The mean ± SD number of valid readings was 45 ± 4 for ABPM1 and 45 ± 5 for ABPM2.

The reproducibility of sleep BP, awake BP, and BP dipping ratio was calculated using the Pearson's correlation coefficient and intraclass correlation coefficient. The reproducibility of nocturnal hypertension, daytime hypertension, any ambulatory hypertension, INH, IDH, DNH, DNN, and BP non-dipping status between ABPM1 and ABPM2 was assessed using the kappa ($K$) statistic and its 95% confidence interval (CI). The reproducibility for any ambulatory hypertension is equivalent to the reproducibility for DNN.

Four sensitivity analyses were performed. First, the $K$ statistic (95% CI) was calculated for nocturnal hypertension, daytime hypertension, any ambulatory hypertension, INH, IDH, DNH, and DNN defining the nighttime and daytime

periods using fixed time periods (12 AM to 6 AM for the nighttime period, and 10 AM to 8 PM for the daytime period) instead of sleep and awake periods.[12] Second, the analyses were repeated after excluding 54 participants who reported taking naps during the daytime period at either ABPM1 or ABPM2. Third, the *K* statistic (95% CI) was calculated for nocturnal hypertension, daytime hypertension, any ambulatory hypertension, INH, IDH, DNH, and DNN using systolic BP and diastolic BP criteria, separately, as defined in the Supplementary Methods. Fourth, in the 246 participants without clinic hypertension, the *K* statistic (95% CI) was calculated for masked nocturnal hypertension, masked daytime hypertension, any masked hypertension, masked INH, masked IDH, masked DNH, and DNN without clinic hypertension.

Statistical analyses were performed using SPSS v.22 (IBM SPSS Statistics for Windows, Version 22.0; IBM, Armonk, NY).

## RESULTS

Supplementary Table S1 shows the sample characteristics (*n* = 282) including mean BP in the clinic, and on ABPM1 and ABPM2. Among the 282 participants, 118 (42%) were male, 60 (22%) were Black, and 169 (60%) were Hispanic. Mean ± SD age and body mass index were 39.4 ± 12.9 years and 27.0 ± 4.9 kg/m$^2$, respectively. Mean ± SD LVMI was 79.4 ± 16.3 g/m$^2$, and LVH was present in 12.4% of participants.

Of the 282 participants, 36 (12.8%) had clinic hypertension. On ABPM1, 76 (27.0%) and 71 (25.2%) participants had nocturnal hypertension and daytime hypertension, respectively. Also, 26 (9.2%), 21 (7.4%), 50 (17.7%), and 185 (65.6%) had INH, IDH, DNH, and DNN, respectively. On ABPM2, 78 (27.7%) and 73 (25.9%) participants had

nocturnal hypertension and daytime hypertension, respectively. Further, 24 (8.5%), 19 (6.7%), 54 (19.1%) and 185 (65.6%) had INH, IDH, DNH, and DNN, respectively. On ABPM1 and ABPM2, 90 (31.9%) and 90 (31.9%) had BP non-dipping respectively.

### Reproducibility of sleep BP, awake BP, and BP dipping ratio

The reproducibility was excellent for awake and sleep systolic and diastolic BP levels, and moderate for BP dipping ratio (Supplementary Table S2).

### Reproducibility of hypertension categories

Table 1 shows the cross-classification of nocturnal hypertension on ABPM1 and ABPM2. The reproducibility of nocturnal hypertension was good: *K* statistic (95% CI) of 0.65 (95% CI 0.55–0.76). Among participants with nocturnal hypertension on ABPM1 (*n* = 76), 58 (76.3%) had nocturnal hypertension on ABPM2. Among participants without nocturnal hypertension on ABPM1 (*n* = 206), 186 (90.3%) did not have nocturnal hypertension on ABPM2.

Table 2 shows the cross-classification of daytime hypertension on ABPM1 and ABPM2. The reproducibility of daytime hypertension was good: *K* statistic (95% CI) of 0.66 (95% CI 0.55–0.76). Among participants with daytime hypertension on ABPM1 (*n* = 71), 54 (76.1%) had daytime hypertension on ABPM2. Of participants without daytime hypertension on ABPM1 (*n* = 211), 192 (91.0%) did not have daytime hypertension on ABPM2.

Table 3 shows the cross-classification of any ambulatory hypertension on ABPM1 and ABPM2. Any ambulatory hypertension had good reproducibility: *K* statistic (95% CI) of 0.72 (95% CI 0.63–0.81).

**Table 1.** Cross-classification of nocturnal hypertension on two 24-hour ambulatory blood pressure monitoring (ABPM) recording periods

| | | Second 24-hour ABPM (ABPM2) | | Reproducibility | |
| --- | --- | --- | --- | --- | --- |
| | | **Nocturnal hypertension** | **No nocturnal hypertension** | **Kappa** | **95% CI** |
| First 24-hour ABPM (ABPM1) | Nocturnal hypertension | **58** | 18 | 0.65 | 0.55–0.76 |
| | No nocturnal hypertension | 20 | **186** | | |

The data are expressed as the number of participants, and kappa statistic with 95% CI. Bolded numbers represent the number of participants with concordant results across the 2 ABPM recordings. Nocturnal hypertension is defined as mean sleep systolic/diastolic blood pressure ≥120/70 mm Hg.

**Table 2.** Cross-classification of daytime hypertension on two 24-hour ambulatory blood pressure monitoring (ABPM) recording periods

| | | Second 24-hour ABPM (ABPM2) | | Reproducibility | |
| --- | --- | --- | --- | --- | --- |
| | | **Daytime hypertension** | **No daytime hypertension** | **Kappa** | **95% CI** |
| First 24-hour ABPM (ABPM1) | Daytime hypertension | **54** | 17 | 0.66 | 0.55–0.76 |
| | No daytime hypertension | 19 | **192** | | |

The data are expressed as the number of participants, and kappa statistic with 95% CI. Bolded numbers represent the number of participants with concordant results across the 2 ABPM recordings. Daytime hypertension is defined as mean awake systolic/diastolic blood pressure ≥135/85 mm Hg.

Table 4 shows the cross-classification of INH, IDH, DNH, and DNN on ABPM1 and ABPM2. Among 26 participants with INH on ABPM1, 7 (26.9%) had INH on ABPM2, and 18 (69.2%) of those with INH on ABPM1 had INH, IDH, or DNH on ABPM2. Further, 6 (28.6%) of the 21 participants with IDH on ABPM1 had IDH on ABPM2. There was poor reproducibility for INH (*K* statistic 0.21; 95% CI 0.04–0.38) and IDH (*K* statistic 0.25; 95% CI 0.06–0.44). Among 50 participants with DNH on ABPM1, 37 (74.0%) had DNH on ABPM2. Among 185 participants with DNN on ABPM1, 167 (90.3%) had DNN on ABPM2. Reproducibility was good for both DNH (*K* statistic 0.65; 95% CI 0.53–0.77) and DNN (*K* statistic 0.72; 95% CI 0.63–0.81).

The reproducibility was moderate for BP non-dipping (Supplementary Table S3) with a *K* statistic (95% CI) of 0.33 (95% CI 0.21–0.45).

### Sensitivity analyses

The reproducibility of ABP phenotypes using fixed time periods to define the nighttime and daytime periods was similar to the analyses for which sleep and awake periods were used (Supplementary Table S4). The results were also similar after excluding 54 participants who reported taking naps (Supplementary Table S5). The reproducibility of each BP phenotype using systolic BP criteria (Supplementary Table S6) and diastolic BP criteria (Supplementary Table S7) was examined separately. When using systolic vs. diastolic BP criteria, the reproducibility of INH was lower, whereas the reproducibility of IDH increased. Finally, among the 246 participants without clinic hypertension, the reproducibility

of masked nocturnal hypertension, masked daytime hypertension, any masked hypertension, masked INH, masked IDH, masked DNH, and DNN without clinic hypertension was similar to the reproducibility of the corresponding BP categories in the entire sample (Supplementary Table S8).

### DISCUSSION

Our primary finding is that INH has poor short-term reproducibility. In contrast, nocturnal hypertension, daytime hypertension, and DNH were reproducible phenotypes. Our study, which to our knowledge is among the first to report the short-term reproducibility of INH, suggests that a single 24-hour ABPM period should not be used to identify individuals with INH.

Nocturnal hypertension is associated with an increased risk of target organ damage, CVD outcomes, and mortality, independent of daytime BP.[2–4,11,13] INH may be an important subtype of nocturnal hypertension, as several studies have shown that it is associated with an increased risk of subclinical CVD, CVD events, and mortality.[2,3,5,14–16] In a population study of 677 Chinese participants, those with INH vs. with DNN had elevated indices of arterial stiffness including central and peripheral augmentation indexes, ambulatory arterial stiffness index, and brachial-ankle pulse wave velocity.[3] Of the participants with INH, 95.6% did not have clinic hypertension.[3] In an analysis of 11 population-based cohorts that included 8,711 participants from Asia, Europe, and South America, Fan *et al.* showed that INH was associated with an increased risk of CVD events (heart rate (HR) 1.38, 95% CI 1.02–1.87) and all-cause mortality (HR 1.29, 95% CI

**Table 3.** Cross-classification of any ambulatory hypertension on two 24-hour ambulatory blood pressure monitoring (ABPM) recording periods

| | | Second 24-hour ABPM (ABPM2) | | Reproducibility | |
| --- | --- | --- | --- | --- | --- |
| | | Ambulatory hypertension | No ambulatory hypertension | Kappa | 95% CI |
| First 24-hour ABPM (ABPM1) | Ambulatory hypertension | **79** | 18 | 0.72 | 0.63–0.81 |
| | No ambulatory hypertension | 18 | **167** | | |

The data are expressed as the number of participants, and kappa statistic with 95% CI. Bolded numbers represent the number of participants with concordant results across the 2 ABPM recordings. Any ambulatory hypertension is defined as daytime hypertension (mean awake systolic/diastolic BP ≥135/85 mm Hg) and/or nocturnal hypertension (mean sleep systolic/diastolic BP ≥120/70 mm Hg).

**Table 4.** Cross-classification of ambulatory blood pressure categories based on nocturnal and daytime hypertension on two 24-hour ambulatory blood pressure monitoring (ABPM) recording periods

| | | Second 24-hour ABPM (ABPM2) | | | | Reproducibility | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | | INH | IDH | DNH | DNN | Kappa | 95% CI |
| First 24-hour ABPM (ABPM1) | INH | **7** | 2 | 9 | 8 | INH: 0.21 | 0.04–0.38 |
| | IDH | 2 | **6** | 7 | 6 | IDH: 0.25 | 0.06–0.44 |
| | DNH | 5 | 4 | **37** | 4 | DNH: 0.65 | 0.53–0.77 |
| | DNN | 10 | 7 | 1 | **167** | DNN: 0.72 | 0.63–0.81 |

The data are expressed as the number of participants, and kappa statistic with 95% CI. Bolded numbers represent the number of participants who were classified in the same category across the 2 ABPM recordings.

Abbreviations: DNH, daytime and nighttime hypertension; DNN, daytime and nighttime normotension; IDH, isolated daytime hypertension; INH, isolated nocturnal hypertension.

1.01–1.65) when compared with DNN.[2] In this study, 79.2% of the individuals with INH did not have clinic hypertension. Finally, in a recent study of 4,608 treated patients with a history of hypertension but who were controlled in the clinic (<140/90 mm Hg), the prevalence of INH was greater than the prevalence of IDH (24.3% vs. 12.9%, respectively).[17] The results of these studies suggest that occult hypertension that only occurs at night and is not seen in the daytime period is associated with increased CVD risk.

Hermida *et al.*[18] demonstrated that individuals with hypertension (*N* = 3,444) randomized to nighttime administration of antihypertensive therapy had significantly lower mean nighttime BP, higher BP decline, reduced prevalence of non-dipping, and a lower risk of CVD events than individuals randomized to morning administration of antihypertensive therapy. Further, lower nighttime BP, associated with antihypertensive medications given at night vs. morning, was associated with a lower risk of CVD events, independent of changes in daytime BP.[18] Whether the cardiovascular benefits of nighttime administration of antihypertensive therapy extends to those with INH remains unknown. The poor reproducibility of INH, as demonstrated in our study, suggests, however, that INH may not be a clinically useful treatment target.

Because ABPM remains the gold standard for diagnosing nocturnal hypertension, characterizing the reproducibility of INH is essential for determining whether individuals in clinical practice should be further characterized as having INH. Studies examining the reproducibility of INH, however, are scarce.[19] The long-term stability of INH was previously studied in 30 Chinese participants who underwent repeat 24-hour ABPM at a mean follow-up of 3.5 years.[3] Among these participants, 10 (33.3%) had INH at follow-up, whereas 10 (33.3%), 2 (6.7%), and 8 (26.7%) were reclassified as having DNH, IDH, and DNN respectively. Whether these results represent the natural history of INH or might be explained by a change in risk factors associated with INH over a long follow-up period is unclear. The current study, which fills an important knowledge gap, indicates that the diagnosis of INH using a single 24-hour ABPM recording period has low short-term reproducibility.

The results of our study also indicate that sleep and awake BP had high reproducibility for both systolic and diastolic BP. These findings are similar to Eguchi *et al.* who demonstrated that sleep and awake BP had good reproducibility among 42 individuals with hypertension who underwent repeat ABPM twice within a 2-week period during an observation period without antihypertensive medication.[20] Further, in our study, the short-term reproducibility of nocturnal hypertension and daytime hypertension were both good, which is similar to prior studies.[21–23] Since the reproducibility of INH and separately IDH depends on the reproducibility of both nocturnal and daytime hypertension, the low short-term reproducibility of INH and IDH, as observed in our study, is not surprising.

In the current study, the reproducibility of any ambulatory hypertension was good. Given that prior studies have shown that daytime hypertension, nocturnal hypertension, and DNH are each associated with an increased risk of CVD

events,[2,24] it may be more advantageous to use ABPM to diagnose any form of ambulatory hypertension, without further classifying individuals into having INH or IDH. In our study, 69.2% of those with INH on ABPM1 were classified as having INH, IDH, or DNH (i.e., any ambulatory hypertension) on ABPM2. This may explain why INH determined on a single ABPM is associated with an increased risk of CVD and mortality[3,5] even though the reproducibility of INH is low.

Finally, the prevalence of INH in our study was 9.2% on ABPM1 and 8.5% on ABPM2. This prevalence is similar to the prevalence of INH reported in prior studies (6.0–10.9%),[3,19] which used a single ABPM recording period to identify INH. Given that INH has low reproducibility, repeat 24-hour ABPM is needed to identify individuals who have INH on both ABPM recording periods. However, the prevalence of INH on both recording periods was only 2.5% (7/282), suggesting that it may not be efficient to screen individuals for INH.

A major strength of this study is that the sample population was community-based and had high minority representation of Hispanics and African-Americans. Additionally, our study included participants who underwent repeat ABPM within a short interval, allowing us to determine the short-term reproducibility of several BP categories.

Our study has several possible limitations. First, our analysis may be limited by the relatively small sample size. Second, our findings may not be generalizable to other populations as our study did not include a high proportion of individuals with diabetes, and individuals with chronic kidney disease were excluded. The reproducibility of INH in populations enriched with individuals with diabetes and/or chronic kidney disease requires further evaluation. Additionally, information regarding nocturia or other reasons for awakening at night, which may impact nighttime BP, was not collected. Lastly, our findings may also not be generalizable to hypertensive patients taking antihypertensive medications.

In conclusion, our findings suggest that INH is poorly reproducible and not a stable phenomenon over the short term. Similar poor reproducibility was found for IDH. In contrast, daytime, nighttime, and any ambulatory hypertension had high reproducibility. These findings have important implications for the risk stratification of individuals using a single 24-hour ABPM recording period. Our results suggest that a single 24-hour ABPM reporting period should be primarily used to identify individuals with daytime hypertension and/or nocturnal hypertension, without further classifying individuals into having isolated forms of ambulatory hypertension including INH and IDH. Our study adds to the growing literature as to how 24-hour ABPM should be used to risk stratify individuals for hypertension-related outcomes.

## SUPPLEMENTARY MATERIALS

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

## ACKNOWLEDGMENTS

## DISCLOSURE

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