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REVIEW

Clinical update

Masked hypertension: understanding its complexity

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Masked hypertension, which is present when in-office normotension translates to out-of-office hypertension, is present in a surprisingly high percentage of untreated persons and an even higher percentage of patients after beginning antihypertensive medication. Not only are persons with prehypertension more likely to have masked hypertension than those with optimal blood pressure (BP), but also they frequently develop target organ damage prior to transitioning to sustained hypertension. Furthermore, the frequency of masked hypertension is high in individuals of African inheritance and in the presence of increased cardiovascular risk factors and disease states, such as diabetes and chronic renal failure. Nocturnal hypertension and non-dipping may be early markers of masked hypertension. Twenty-four hour ambulatory BP monitoring (ABPM), which can detect nighttime and 24 h elevated BP, remains the gold standard for diagnosing masked hypertension. Almost one-third of treated patients with masked hypertension remain as 'masked uncontrolled hypertension', and it becomes important, therefore, to use ABPM (and supplemental home BP monitoring) for the effective diagnosis and control of hypertension.

Keywords Masked hypertension • Ambulatory blood pressure monitoring • Hypertension • Masked uncontrolled hypertension • Cardiovascular disease • Nocturnal hypertension • Dipping status

Introduction

We reviewed the current literature on masked hypertension, including definitions and terminology, special high prevalent populations at risk, mechanisms of production, masked naïve hypertension vs. treated but uncontrolled hypertension, and diagnostic and treatment strategies. Our searches for masked hypertension consisted of PubMed references from its original description in 2002 through April 2016 using key words of masked hypertension, isolated ambulatory hypertension, white coat normotension, and reversed white coat hypertension. We reviewed articles in English identified in these searches and relevant references cited in these articles that were specifically related to our subheadings (682 published papers). The final selection of references was limited to about 50, as prescribed by JACC guidelines for reviews.

Definitions and terminology

Blood pressure (BP) is a continuous variable with no specific separation between normal and abnormal values. However, there are specific BP thresholds that enable physicians to make diagnostic, prognostic, and therapeutic decisions. In-office hypertension is defined arbitrarily by a conventional BP of ≥140/90 mmHg. Similarly, there is a spectrum of values for out-of-office BP. In contrast to in-office BP values, out-of-office values can be defined for any single one or combination of time intervals.[1] Current consensus guidelines define out-of-office daytime hypertension as BP ≥135/85 mmHg, nighttime as BP ≥120/70 mmHg, and 24 h average as BP ≥130/80 mmHg.[1] Indeed, the 24 h period can be further subdivided into the white coat window (generally the first hour and possibly also the last hour) when the patient is under the influence of the medical

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Table 1 Ambulatory and home blood pressure values (mmHg)

	Interval	Optimal (mmHg)	Normal (mmHg)	Elevated (mmHg)
ABPM (consensus)	Daytime	<130/80	<135/85	≥135/85
(Pop.-based)	Daytime	<120/75	<125/80	≥130/85
Home (consensus)	Daytime	<130/80	<135/85	≥135/85
(Pop.-based)	Daytime	<120/75	<125/80	≥130/85
ABPM (consensus)	Nighttime	<115/65	<120/70	≥125/75
(Pop.-based)	Nighttime	<100/65	<110/70	≥120/70
ABPM (consensus)	24 h	<125/75	<130/80	≥135/85
(Pop.-based)	24 h	<115/75	<125/85	≥130/80

Consensus and pop.-based denote consensus-based and population-based threshold, respectively. ABPM (population-based);[1] ABPM (consensus-based);[2] Home (consensus-based);[3] and Home (population-based).[3] ABPM, ambulatory blood pressure monitoring.

environment.[1] The daytime cut-points for hypertension pertain to both ABPM and home BP monitoring (HBPM). Thus, for daytime measurements, the definition of masked hypertension in untreated individuals is an in-office BP of <140/90 mmHg and out-of-office BP of ≥135/85 mmHg. Furthermore, HBPM, lacking nighttime and 24 h BP readings, would fail to diagnose many individuals with masked hypertension. When referring to untreated persons, the term masked hypertension is appropriate, whereas when referring to persons receiving antihypertensive treatment, the diagnosis of masked hypertension by definition is known; therefore the term *masked uncontrolled hypertension* (frequently abbreviated MUCH) is preferred and implies that further treatment is necessary for optimal BP control.[1]

It should be noted, as shown in *Table 1*, that population-based ABPM and HBPM cutoff values are general lower than consensus-based numbers, mainly reflecting the importance of cardiovascular risk in masked hypertensives that are contained predominantly in those persons with prehypertension and occasionally with optimal BP.[2,3] Using optimal BP (<120/<80 mmHg) vs. prehypertension (130–139/80–89 mmHg) as Joint National Classification BP categories, these guidelines detected 7.5% and 29.3% of subjects with masked hypertension, respectively (*Figure 1*).[4] However, randomized controlled trials would be necessary to prove that screening procedures for the decision to begin antihypertensive drug treatment would reduce the incidence of cardiovascular events sufficiently to be cost-effective.

Screening methods

Screening conventional office measurements provides moderately good prediction of masked hypertension in persons with prehypertension.[1,4] Pickering *et al.*,[5] who first described this entity, believed that masked hypertension, often alternating with prehypertension, was a precursor to sustained hypertension. On one hand, a 4 week Chinese study, using daytime BP of 130/80 mmHg as a threshold, confirmed the persistence of masked hypertension or progression to sustained hypertension (odds ratio per 1 SD increase, 3.49, 95% CI,1.06–11.2; $P = 0.04$).[6] On the other hand, a 5 year population study in Quebec, assessing the persistence of masked hypertension and its progression to sustained hypertension,[7] showed that in persons with masked hypertension at baseline, more than half had either masked or sustained hypertension at 5 years. Many of these persons with masked hypertension had been started on antihypertensive treatment; one-third progressed to sustained hypertension, one-third regressed to normotension, and one in five remained masked over 5 years when not treated.[7] Importantly, delay in making the diagnosis of masked hypertension may account for the high prevalence of hypertensive target organ damage.[8,9] Moreover, both untreated patients with masked hypertension and treated patients with masked uncontrolled hypertension had evidence of persistent hypertensive target organ damage that is comparable to what is observed in persons with sustained hypertension, especially when non-dipping occurs in combination with nocturnal hypertension.[8,9]

Mechanisms leading to masked hypertension

Environmental factors

Conventional office measurement of BP in an elderly hypertensive persons soon after a large meal may demonstrate a postprandial reduction of BP and in these subjects, a diagnosis of masked hypertension is more likely.[10] Persons who are subject to mental stress at work or at home may have normal BP at the time of office measurement with elevated pressure only being manifested by ABPM during the stressful circumstances.[11] Smokers and persons that consume excessive alcohol are prone to masked hypertension.[12,13] Sedentary, obese, individuals may have poor exercise tolerance throughout the day's activities, whereas pre-hypertensive BP values may be recorded in the physician's office when measured at rest.[14] Furthermore, advanced age, associated with decreased baroreceptor sensitivity and increased BP variability, results in a higher prevalence of masked hypertension with a male predominance.[15] Shortened sleep time[1] often starting in adolescents[16] and obstructive sleep apnoea have been associated with nocturnal hypertension and masked hypertension.[17]

Masked daytime vs. nighttime hypertension

Yano and Bakris[18] have suggested that masked hypertension may be classified on the basis of masked daytime vs. masked nighttime

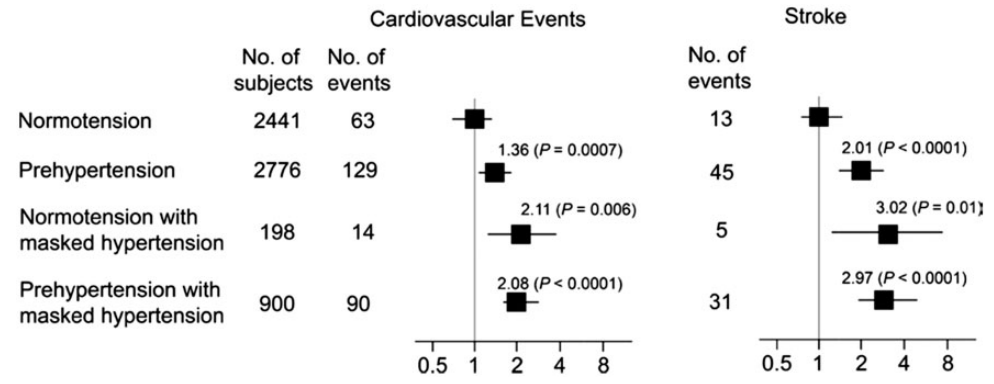

Figure 1 Hazard ratios (HRs) for cardiovascular events and strokes associated with masked hypertension in subjects with normotension (<120/<80 mmHg) or prehypertension (120–139/90–89 mmHg) according to their conventional blood pressure.[4] Participants with sustained normotension are the reference group. HRs are obtained from the KDACO database and are adjusted for cohort, sex, age, body mass index, smoking and drinking, cholesterol, diabetes, and history of cardiovascular complications (with permission from Brguljan-Hitij *et al.*[4]).

patterns. For example, one group shows predominantly selective daytime masked hypertension when exposed to job strain, mental stress, smoking, heavy drinking, or poor exercise tolerance. In contrast, a second group presents with predominantly nocturnal masked hypertension in the presence of sleep deprivation, obstructive sleep apnoea, metabolic syndrome, diabetes, or chronic kidney disease (CKD).[18] Of course, many persons with masked hypertension will display both daytime and nighttime masked hypertension.

Indeed, there is long-standing evidence that nocturnal hypertension plays an important role in both masked and sustained hypertension.[19–21] Despite the potential overlap between prehypertension and masked hypertension, there are important distinctions between the two entities: persons with masked hypertension may present with isolated nocturnal hypertension, especially in the presence of increased cardiometabolic risk.[19–21]

The mechanisms by which nocturnal hypertension contributes to masked hypertension may be secondary to increase sympathetic nerve activity as shown by Grassi *et al.*[22] These investigators showed that there were increased bursts of sympathetic nerve activity with elevated out-of-office elevation in BP, whereas in-office BP was within normal limits.[22]

The Ambulatory Blood Pressure Collaboration in Patients with Hypertension meta-analysis of 17 312 hypertensive patients from three continents has confirmed the prognostic importance of nocturnal hypertension in sustained hypertension and in masked hypertension.[23] This meta-analysis demonstrated that a blunted nocturnal BP decline, both as a mean nighttime sleep entity and as a categorical non-dipping subgroup, were predictors of worse cardiovascular outcomes, independent of average ambulatory 24 h BP levels.[23] However, randomized controlled studies are needed to test the hypothesis that reestablishing normal dipping patterns with antihypertensive treatment in patients with sustained hypertension and masked uncontrolled hypertension will be associated with reduced future cardiovascular events.

Populations of high-prevalence masked hypertension

The prevalence of masked hypertension varies considerably, depending on population characteristics. Antihypertensive treatment almost invariably further increases the frequency of masked hypertension.

Persons of African inheritance

With the use of ABPM, masked hypertension has been identified in more than one-third of untreated African Americans[24,25] and more than 40% of low-income South Africans.[26] These high rates of masked hypertension in persons of African inheritance support early ABPM screening, especially in the presence of high-normal BP. In the Jackson Heart Study of African Americans, 19% of subjects had isolated nocturnal hypertension by ABPM at a time when the mean office BP was 124/76 mmHg.[24] Furthermore, these persons had greater left ventricular mass compared with normotensives as well as three times the odds of left ventricular hypertrophy (LVH).[24] In a more recent Jackson Heart Study, conducted in 972 African Americans, masked hypertension was noted in 34% of untreated participants with normal clinic BP.[25] Male gender, smoking, diabetes, and antihypertensive treatment were predictors of masked hypertension in multivariate analysis.[25] In the open-treatment phase of the African American Study of Kidney disease and Hypertension (AASK) trial, 70% of patients with treated but uncontrolled masked hypertensives had nocturnal non-dipping or reverse-dipping pattern and hypertensive target organ damage despite controlled clinic BP.[27]

Diabetes

One-third of Korean juvenile type-1 diabetics showed carotid intima-media thickness in association with masked hypertension;[28] this study underscores the importance of ABPM in detecting nocturnal hypertension as the first manifestation of altered BP.[28] In a Brazilian study of type-2 diabetics presenting with prehypertension, 30% had

untreated masked hypertension and significant echocardiographic diagnosis of LVH and macro-proteinuria as compared with sustained normotensive controls.[29] Similarly, in an untreated IDACO population, masked hypertension was present in 29% of type-2 diabetic subjects as compared with 19% in an age, sex, and risk-factor adjusted non-diabetic masked hypertensive population.[30] In the treated IDACO population, 42.5% of diabetics presented with masked uncontrolled hypertension, suggesting inadequate antihypertensive treatment in these patients.[30]

Chronic kidney disease

In children with CKD, LVH was four times more frequent in the presence of masked hypertension as compared with those with normal ABPM.[31] Furthermore, Agarwal *et al.*[32] showed that nearly 60% of treated patients with CKD had masked uncontrolled hypertension, which was diagnosed exclusively 24% of the time by nighttime ABPM. The prevalence of masked uncontrolled hypertension was present in 66% in patients with high-normal clinic systolic BP (SBP), 33% in normal clinic SBP, and only 17% with optimal clinic SBP; thus, patients with CKD and pre-hypertension warrant ABPM screening to identify masked uncontrolled hypertension.[32] Moreover, in the Chronic Renal Insufficiency Cohort Study, not only was the prevalence of untreated masked hypertension high (28%), but also subjects identified by nocturnal hypertension and reduced estimated glomerular filtration rate had evidence of prolonged age-adjusted aortic-femoral pulse wave velocity indicative of increased arterial stiffness.[33]

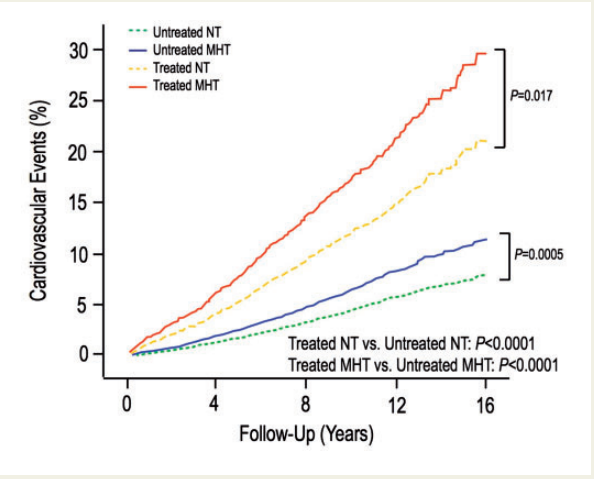

Figure 2 Cohort, sex, and age-standardized incidence of cardiovascular events in untreated and treated normotensive (NT) and masked hypertensive (MHT) non-diabetic subjects that are derived from an IDACO meta-analysis.[17] Fully adjusted, hazard ratios for treated vs. untreated masked hypertensives are as follows: hazard ratio, 2.27 (95% CI, 1.6–3.2; $P < 0.0001$) (adapted from Franklin *et al.*[30]).

The significance of masked uncontrolled hypertension

Why is the prevalence of masked uncontrolled hypertension higher in treated vs. untreated persons?

It is well established that antihypertensive treatment will not lower ABPM values as much as in conventional office BP; for example, a 3 mmHg SBP reduction of in-office BP equates roughly to 2 mmHg SBP reduction in ABPM.[34] The mechanisms responsible for this '3 to 2 ratio' of SBP reduction with treatment are not altogether clear, but appear to be complex. A morning recording of normal in-office BP may coincide with peak levels of medication, whereas trough levels later in the day and/or night may be associated with hypertensive BP values, a phenomenon that is especially evident when insufficient doses are prescribed. Indeed, Pareek *et al.*[35] showed that after 12 weeks of low-dose 12.5 mg of hydrochlorothiazide given daily to 20 patients with sustained hypertension, 24 h ABPM disclosed that the majority was converted into masked uncontrolled hypertension, rather than the desired conversion to sustained normotension. Furthermore, Schmieder *et al.*[36] noted that patients with higher pre-treatment SBP levels had an even greater disproportional reduction in office than in ambulatory SBP in association with antihypertensive treatment; this concept dates back to the so-called Wilder's principle, whereby pre-treatment BP is a determinant of antihypertensive response;[37] There are still other possible explanations: increased prevalence of masked uncontrolled hypertension may be an indication of patient non-compliance with medication, except just prior to visiting the physician's office. Regardless of the mechanism for the greater reduction in office than in ABPM, the important message for physicians is that treatment aimed at normalizing conventional office BP, while ignoring out-of-office BP, may increase the percentage of patients with masked uncontrolled hypertension.[30]

Why does treatment increase the cardiometabolic risk in masked uncontrolled hypertension?

The effects of antihypertensive treatment vs. no treatment on the prevalence of sustained hypertension, masked hypertension, and sustained normotension in a non-diabetic population have been clearly demonstrated in a recent adapted IDACO study (*Figure 2*).[30] Not only did antihypertensive treatment increase the prevalence of masked uncontrolled hypertension (see also *Table 2*), but it also increased cardiovascular risk in patients with this entity and in treated sustained normotensives (*Figure 2*).[30] The logical explanation for these findings is that some patients with sustained hypertension were *converted* into masked hypertension and some patients with masked hypertension were *converted* into sustained normotension. Thus, there was increased cardiometabolic risk in both treated patients with masked uncontrolled hypertensives and in those with sustained normotensive patients in comparison to the untreated patients with either masked hypertension or sustained normotension, respectively.[30] These findings illustrate the epidemiological principle that normalization of BP with treatment does not eliminate the lifetime burden associated with prior elevation of BP, nor does it correct the other cardiometabolic risk factors that are associated with the hypertensive state. Therefore, antihypertensive treatment initiates a *transformational change* from sustained hypertension to masked uncontrolled hypertension and finally to sustained normotension.[30]

Table 2 Prevalence of masked hypertension by treatment status in diabetics and non-diabetics

Treatment status	Prevalence (%)		Odds ratio		
	Non-diabetics	Diabetics	Unadjusted	Partly adjusted	Fully adjusted
Untreated	18.8% (1031/5486)	29.3% (67/229)	1.79 (1.33–2.40) $P<0.001$	1.46 (1.08–1.98) $P=0.014$	1.35 (0.98–1.86) $P=0.065$
Treated	30.5% (192/630)	42.5% (37/87)	1.69 (1.07–2.67) $P=0.025$	1.59 (1.00–2.52) $P=0.051$	1.59 (0.98–2.58) $P=0.058$

Partly adjusted odds ratios are adjusted for sex and age only. Fully adjusted odds ratios are adjusted for sex, age, conventional systolic blood pressure, history of cardiovascular complications, current smoking status, current alcohol intake, body mass intake, and total cholesterol. This table is taken from Franklin *et al.*[33]

The cardiometabolic risk in a patient with treated, *normalized* BP (both in- and out-of-office) is therefore always greater than a non-treated person with an identical BP.

Role of physicians in the prevention and management of masked hypertension

The high prevalence of masked uncontrolled hypertension among treated subjects suggests that many physicians prescribe 'suboptimal' antihypertensive treatment; this may be due in part to physician inertia, failure in selecting long-acting antihypertensive medications, and in part to confusion as to the optimal treatment goals in patients with high cardiometabolic risk. The recent publication of the Systolic Blood Pressure Intervention Trial (SPRINT), which measured BP with an automated, in-office device to limit white coat effect, favoured a treatment goal of ~120 mmHg SBP rather than the traditional goal of <140 mmHg in order to minimize cardiovascular disease (CVD) events in an older aged, high-CVD-risk population.[38] Kjeldsen *et al.*,[39] in analysing the results of the SPRINT study, concluded that the BPs taken in SPRINT could not be directly compared with BPs recorded by conventional clinic methods in other randomized controlled trials; they reasoned that the 120 mmHg treatment arm of SPRINT translates into ~<135 mmHg, currently recommended by most treatment guidelines.[39] The irony of this comparison is that what works well for several thousand subjects in a randomized controlled trial does not translate into what is optimal BP for the single patient! Unfortunately, if physicians continue to use conventional office measurement of BP, this will result in the unnecessary treatment of older patients with low-risk white coat hypertension and the failure to diagnose high-risk masked hypertension in many elderly patients with isolated systolic hypertension. Furthermore, in the absence of ABPM and/or HBPM use, physicians will undertreat masked uncontrolled hypertension in a significant number of patients. In contrast, optimal treatment of masked hypertension, which frequently requires the use of combination antihypertensive drug therapy and out-of-office BP monitoring, has the best chance of achieving sustained normotension without overtreatment.[40]

By the same token, however, the use of ABPM may play an important role in setting limits on how low to go in controlling BP with antihypertensive treatment. As outlined in the European Society of Hypertension/European Union of Geriatric Medicine Expert Opinion Report,[41] there may be limits or even contraindications to the use of antihypertensive therapy in the very old, defined as ≥80 years of age or in the presence of frailty, in part confirmed by an ABPM diagnosis of orthostatic hypotension at some time during the 24 h cycle.[41] These guidelines were reinforced by a recent study defining treatment thresholds for HBPM in octogenarians by the International Database on Home Blood Pressure in Relation to Cardiovascular Outcome (IDHOCO) investigators.[42]

Diagnostic strategies for masked hypertension

Although automated office monitoring of BP is far superior to conventional office measurements in decreasing the misleading white coat effect[43] and should replace conventional office measurement when feasible, it cannot replace out-of-office methods of measurements. HBPM has the advantage of detecting many patients with masked hypertension,[44] but a Chinese study using HBPM in comparison with ABPM, failed to diagnose masked hypertension in more than 25% of patients, thus confirming the superiority of ABPM over HBPM.[45] Indeed, a meta-analysis done by Hodgkinson *et al.*[46] concluded that neither conventional office BP measurement nor HBPM had sufficient sensitivity or specificity to replace ABPM as the reference standard. Consequently, British NICE treatment recommendations for cost-effectiveness favour confirming a conventional office/clinic diagnosis of hypertension with ABPM before beginning antihypertensive therapy.[47] After extensive analysis of the diagnostic and predictive accuracy of BP screening, the US Preventive Services Task Force concluded that ABPM is the diagnostic method of choice for detecting both outliers of white coat and masked hypertension.[48]

Treatment strategies for masked and uncontrolled masked hypertension

In a Spanish Registry study in which 2115 treated hypertensive patients were followed over 4 years for cardiovascular events, after adjustment for baseline cardiovascular risk and office BP, nighttime

but not daytime SBP predicted cardiovascular events (hazard ratio per SD increase, 1.45: 95% CI, 1.29–1.59)' thus, nighttime BP was the single most important predictor of cardiovascular risk.[49] Using an updated database from the Spanish Registry, 31% of patients were identified as having masked uncontrolled hypertension by ABPM among the 14 840 subjects whose BP appeared to be controlled with conventional BP measurements.[50] The clinical characteristics of masked uncontrolled hypertensive patients were male sex, advanced age, obesity, smoking history, diabetes, and longer duration of hypertension—all of which increased the risk of future CVD.[50] Importantly, poor control of nocturnal BP was twice as frequent as poor daytime ABPM control; indeed, isolated nocturnal hypertension occurred in 24% of these patients. Therefore, this study favoured the use of ABPM to monitor BP control during antihypertensive treatment, both during daytime and at night, and especially in high-risk patients.[50] As noted above, there is strong evidence that patients with masked hypertension have increased risk of target organ damage and cardiovascular morbidity approaching that of sustained hypertensives. Furthermore, many persons with masked hypertension have additional cardiometabolic risks, such as diabetes, obstructive sleep apnoea, and CKD that require additional management to supplement antihypertensive treatment. Rather than a placebo-controlled trial in the presence of target organ damage in patients with masked hypertension, there is need for a randomized controlled trial that assesses the optimal level of daytime and nighttime BP reduction in order to weigh therapeutic benefits in preventing heart attacks, strokes, and other major cardiovascular and renal complications of hypertension.

Perspectives

Masked hypertension, defined as office normotension with conventional BP measurements and out-of-office hypertension in persons not receiving antihypertensive treatment, has overall cardiovascular risk equivalence to Stage-1 hypertension. Masked hypertension is frequently associated with target organ damage, such as LVH and proteinuria—often long before a transition from the masked stage to sustained hypertension. Importantly, initiating antihypertensive treatment based only on conventional office BP may have the effect of converting many patients with sustained hypertension into masked uncontrolled hypertension, rather than having the desired therapeutic goal of sustained normotension. ABPM is the preferred diagnostic method of assessing out-of-office BP during the initiation and titration of antihypertensive therapy. HBPM can be a valuable supplement to ABPM (or an alternative if ABPM is not available). The two methods record BP differently and tend to complement each other in confirming cardiometabolic risk, but ABPM is the method of choice because it provides nighttime BP recording and may better define the overall risk of masked uncontrolled hypertension. Importantly, undiagnosed and untreated masked hypertension and treated but uncontrolled masked hypertension represent two significant high-risk populations of public health concern. Indeed, current evidence must now surely make it mandatory that National and International guidelines, which currently base diagnostic and therapeutic decisions on conventional in-office BP measurements, should now recommend that all patients who have had elevated BP recorded by conventional measurement must now have ABPM (and if not available, HBPM) in order to determine the true level of BP and ultimately improve the current worldwide poor control rates of hypertension.

Conflict of interest: none declared.

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