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Current challenges for hypertension management: From better hypertension diagnosis to improved patients' adherence and blood pressure control

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ABSTRACT

Hypertension control still remains a largely unmet challenge for public health systems. Despite the progress in blood pressure (BP) measurement techniques, and the availability of effective and safe antihypertensive drugs, a large number of hypertensive patients are not properly identified, and a significant proportion of those who receive antihypertensive treatment fail to achieve satisfactory control of their BP levels. It is thus not surprising that hypertension is still a major contributor to disease burden and disability worlwide, even in developed countries. This paper will address current challenges in hypertension management and potential strategies for an improvement in this field. In its first part relevant issues related to hypertension diagnosis will be addressed, in particular how to improve identification of sustained BP elevation and specific BP phenotypes such as white coat and masked hypertension trough the combined use of office and out-of-office BP monitoring techniques. In its second part focus will be on how to improve achievement of hypertension control in treated patients by optimization and simplification of medication regimens, including more efficient selection and titration of antihypertensive drugs and their combinations, aimed at achieving a more consistent 24hBP control; and by favoring a more active patients' and physicians' involvement in hypertension management also through BP telemonitoring and mobile health technologies.

1. Introduction

Hypertension is a major cardiovascular risk factor, contributing significantly to cardiovascular disease burden and disability worldwide [1–3], but its control remains a largely unmet challenge for public health systems. Despite the progress in blood pressure (BP) measurement techniques, and the availability of effective and safe antihypertensive drugs, these tools are not always optimally used in clinical practice. As a consequence, a large number of hypertensive patients are not properly identified, and a significant proportion of those who receive antihypertensive treatment fail to achieve effective control of their BP levels. This translates into an increased risk of morbidity and mortality due to hypertension-related cardiovascular complications [4,5]. This paper is aimed at addressing relevant current challenges in hypertension management and potential strategies for an improvement in this field, with particular focus on: 1) how to improve hypertension diagnosis by a proper identification of elevated BP values and specific BP phenotypes (through the combined use of office and out-of-office BP monitoring), such as white coat and masked hypertension; and 2) how to improve achievement of hypertension control in treated patients by optimization and simplification of medication regimens, including more efficient selection and titration of antihypertensive drugs and their combinations, aimed at achieving a more consistent 24hBP control (i.e. troughout day and night); and by favoring a more active patients' and physicians' involvement in hypertension management. In such a context, particular attention is given to the role of ambulatory (ABPM) and home BP monitoring (HBPM), BP telemonitoring and mobile health technologies, which may allow not only to quantify different BP patterns known to have prognostic relevance, such as nocturnal dipping, morning rise, enhanced 24h, day-to-day or visit-to-visit BP variability, and masked hypertension phenomena, but also to improve patients' adherence/compliance to antihypertensive treatment and patient–physician interaction [6,7].

1.1. Improvement of hypertension diagnosis by identification of different blood pressure phenotypes through combined use of office and out-of-office BP monitoring

Although office BP (OBP) measurement is still the most common used technique for screening and diagnosis of hypertension, it is intrinsically inaccurate and importantly influenced by measurement errors

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and observer's bias. OBP measurements are also affected by a random error, related to the fact that spot BP assessment during consultation does not faithfully reflect subjects' exposure to BP load in real life conditions. As acknowledged in several hypertension guidelines [4,5,8–14], management of hypertension is largely sub-optimal when based only on OBP measurements, which has stimulated the introduction of out-of-office BP monitoring methods, including ambulatory BP monitoring (ABPM) and home BP monitoring (HBPM). Thanks to progress in technology and to the availability of standardized validation protocols, [15] both ABPM and HBPM have been increasingly used over the last decades in clinical practice, either for accurate hypertension diagnosis and for improving BP control rates in treated hypertensive subjects.

In recent years, with the attempt to improve BP assessment in the office, automated unattended office BP (AOBP) measurement has been proposed as a method allowing more accurate management of hypertensive patients and prediction of hypertension-mediated target organ damage (HMOD) [16]. This approach, which involves multiple BP readings taken with a fully automated device in absence of health care personnel after the patient has been resting quietly alone for a few minutes, has been in particular proposed to avoid the white coat effect (WCE) [16]. In fact, preliminary studies indicate that the WCE associated with conventional attended office BP measurements can be virtually eliminated by recording AOBP. However, a number of issues related to AOBP still need to be clarified, including its actual ability to predict outcome better than other BPM methods. There is also limited information on the relation of AOBP with ABPM and with conventional attended office BP measurement, an issue currently being explored by ongoing studies with the primary goal of quantifying the WCE by comparing different BP measuring techniques [17].

As illustrated in Fig. 1 combined use of office and out-of-office blood pressure (BP) measurements allows identification of a number of specific BP patterns, characterized by discrepant levels of office and out-of-office BP. In untreated patients, these conditions are defined as white coat hypertension (WCH, elevated office and normal out-of-office BP), or masked hypertension (MH, normal office and elevated out-of-office BP), respectively. In treated patients, these conditions are defined as white coat uncontrolled hypertension (WCUH, with uncontrolled office and normalized out-of-office BP), and masked uncontrolled hypertension (MUCH, with normalized office and uncontrolled out-of-office BP in spite of treatment), respectively. These different hypertension phenotypes are increasingly acknowledged to have clinical relevance, often leading to diagnostic errors and to over- or under-treatment, respectively [18–20]. Evidence has been provided in this regard showing that both WCH and MH in untreated individuals and WCUH and MUCH in treated patients are associated to an increased risk of major cardiovascular outcomes and hypertension related hospitalization [21,22].

Most of the advantages of ABPM come from its ability to provide a large number of measurements over the 24h and from the possibility to obtain BP measurements in subjects' daily life, both during wakefulness and during sleep. Although indications for ABPM are becoming progressively wider, based on the evidence that a larger use of ABPM could contribute to reduce healthcare costs, better predict cardiovascular events and be life-saving, [23] even in developed countries use of ABPM is at present still recommended in selected cases only.

From a practical perspective, whenever ABPM is not available, difficult to access or not well tolerated by patients, some of its advantages can be nevertheless obtained through use of HBPM. Average HBP values are more reproducible than OBP and as reproducible as average ABP values, or even better. The better reproducibility of average HBP levels is related to the inclusion of a higher number of readings in its assessment. Indeed, HBPM has experienced an exponential diffusion in recent years, due to progress in technology leading to the availability of small, accurate, user-friendly and relatively inexpensive BP monitoring devices [24,25]. Both HBPM and ABPM can identify the white-coat and masked hypertension phenomena in untreated and treated individuals and the same threshold is recommended for diagnosing hypertension by average home and daytime ambulatory BP [5,4,10]. These similarities of HBPM and ABPM are probably due to the fact that both methods provide multiple measurements taken away from the office setting in the usual living environment of a given individual. However, there are important methodological differences between them, as home BP is recommended to be measured after a few minute rest, in a standardized sitting posture, at home and during the wake time, whereas ambulatory BP is measured in different non standardized postures (sitting, standing and lying), in different environments (work, home, other) and during routine daytime activities and nighttime sleep. In this context, the importance of offering proper education to patients on the correct way to implement HBPM has to be emphasized, given that in real life self-BP measurements are often performed during or soon after stressful

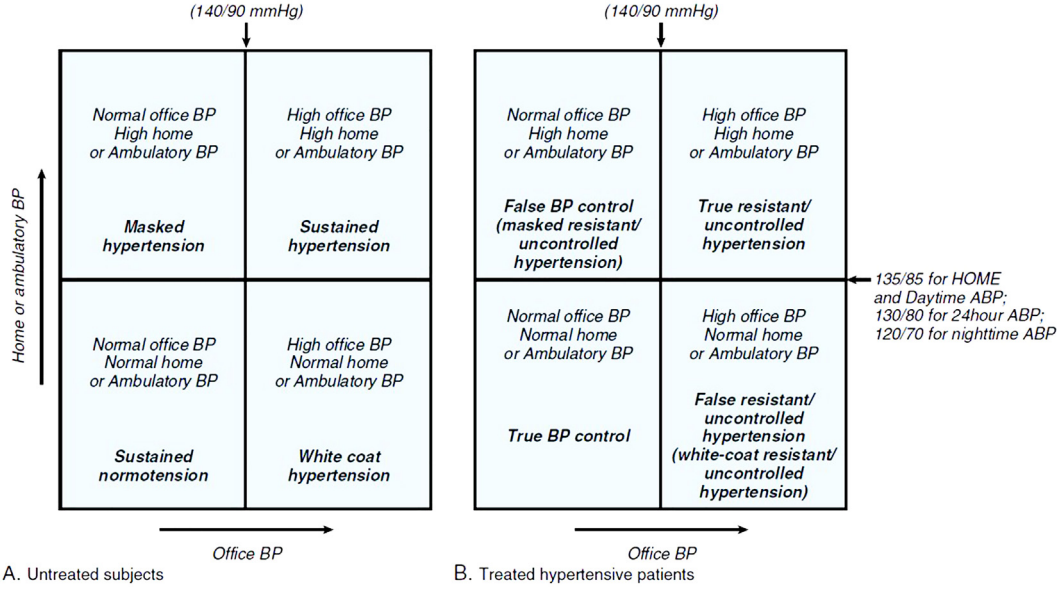

Fig. 1. Definition of different blood pressure (BP) phenotypes, based on variable combination of office and ambulatory (A) or home (H)BP levels in untreated subjects (left panel) and in treated hypertensive patients (right panel), respectively. Taken from Parati et al. [20] by permission.

conditions or illness, which might lead to report high BP values not representative of patients' usual BP levels.

Thus, HBPM and ABPM are similar but are not identical methods and the diagnostic agreement between them is still a challenging clinical issue. In this context the imperfect reproducibility of HBP and ABP data obtained at different times, and that of the derived phenotypes, should also be considered [26].

In most current hypertension guidelines, both HBPM and ABPM are recommended in order to improve diagnosis and management of hypertension [4,5,8–12], [1314](see Table 1) with indication to use them as complementary and not as alternative diagnostic methods.

2. Improvement of hypertension control

Despite the availability of a wide range of safe and effective antihypertensive drugs, that can be used alone or in combination to control hypertension in the majority of individuals requiring treatment, hypertension management remains suboptimal. Recent reports indicate that BP control remains far from adequate regardless of global location, with only 60% of treated subjects achieving control of their BP values [29]. Major causes for this failure include poor patients' adherence to long-term therapy and therapeutic inertia (defined as failure by a physician to titrate or modify antihypertensive therapy in the setting of identified poor BP control) [30]. Low adherence to antihypertensive treatment is the most common cause of treatment resistance [31] and is associated with an increased risk of cardiovascular morbidity and mortality [32]. According to a large meta-analysis of prospective epidemiological studies, about 9% of cardiovascular disease events may be attributable to poor adherence to cardiovascular medications [33]. The factors driving to non-adherence in a given patient can vary depending on the patient's profile, including fear of possible or experienced adverse events, lack of information, actual or perceived lack of treatment benefit, forgetfulness, complexity of dosing regimen and polypharmacy [34]. On the other hand, physician's inertia, i.e. the failure to initiate therapy or to intensify or change therapy in patients with elevated BP values, and a poor patient–physician communication are also contributing factors for failure to achieve BP targets [35]. It should be noted that, therapeutic inertia is also influenced by factors related to the healthcare system, time constraints and workload pressure placed on physicians. As mentioned above, BP control may be suboptimal also when its assessment is based on OBP values only. A series of strategies such as simplifying the therapeutic regimen, use of HBPM for the long-term follow-up of hypertensive patients, implementation of telemonitoring of home BP values or use of mobile health technologies for HBP telemonitoring, might offer an opportunity to overcome these problems.

2.1. Use of HBP monitoring for treatment titration

Titration of antihypertensive treatment is a crucial part of the management of hypertensive patients. However, titration on the basis of OBP measurements in primary care may be suboptimal. HBPM offers the unique possibility to repeatedly evaluate BP on treatment over prolonged time intervals, and thus to titrate BP medications based on a higher number of readings. A series of recent studies [36] have indicated that optimization of number and dose of antihypertensive medications on the basis of HBPM is associated with better BP control rates. The TASMINH4 and TASMIN-SR studies, have also shown that patients can also use self-monitored BP to self-titrate their own antihypertensive medication successfully following adequate education, which also translates into improved BP control rates [37,38]. Recent meta-analyses have indicated that self-monitoring alone is not associated with lower BP values or with better BP control rates, while this can be achieved when HBPM is implemented in conjunction with co-interventions (including systematic medication titration by doctors, pharmacists, or patients; patients education or lifestyle counselling)

Table 1
Current Recommendations on the Clinical Use of Office and Out-of-Office BP Measurement in Different Hypertension Guidelines (AHT = Antihypertensive treatment; HT = Hypertension; OBP = office BP; AOBP = automated unattended office BP; ABPM = ambulatory BP monitoring; HBPM = home BP monitoring).

Guidelines	In office BP (OBP and AOBP)	Out of office BP (ABPM and HBPM)
2017 AHA/ACC [4] (American Heart Association/American college of Cardiology)	For diagnosis and management of high BP, OBP measurement is recommended for accurate measurement and documentation of BP	Out-of-office BP measurements are recommended to confirm the diagnosis of HT and for titration of BP-lowering medication, in conjunction with telehealth counselling or clinical interventions. Primary role to HBPM particularly in treated hypertensives, given its much wider availability in primary care and better acceptance by users for long-term application.
2018 ESH/ESC [5],(European Society of Cardiology/European Society of Hypertension)	When hypertension is suspected because of an elevated screening BP, the diagnosis of HT should be confirmed by repeated OBP measurements over a number of visits.	These guidelines also support the use of out-of-office BP (i.e. HBPM and/or ABPM) as an alternative strategy to repeated office BP measurements, to confirm the diagnosis of HT, when these measurements are logistically and economically feasible. ABPM and HBPM indicated in particular situations: Conditions in which WCH and MH are more common, postural and post-prandial hypotension, evaluation of resistant HT, evaluation of BP control, exagerated BP response to exercise, considerable variability in OBP, evaluating symptoms consistent with hypotension during treatment. Specific indications for ABPM rather than HBPM: Assessment of nocturnal BP values and dipping status (e.g. suspicion of nocturnal hypertension, such as in sleep apnoea, CKD, Diabetes, endocrine HT, or autonomic dysfunction)
2020 (accessed) NICE [27] (National Institute for Health and Care Excellence, UK)	If OBP is ≥140/90 mmHg ABPM has to be offered to confirm HT. OBP to monitor the response to AHT treatment.	ABPM is indicated to confirm the diagnosis of hypertension when OBP is ≥140/90 mmHg. HBPM is a suitable alternative to confirm the diagnosis of hypertension when ABPM is not available. ABPM or HBPM as possible adjunct to OBP to monitor the response to antihypertensive treatment in the presence of WCE.
2020 Hypertension Canada's [13]	Standardized BP measurement (both OBP and AOBP are recommended and, using	Use of out-of-office measurement (24-h ABPM or HBPM) is recommended for all

Table 1 (*continued*)

Guidelines	In office BP (OBP and AOBP)	Out of office BP (ABPM and HBPM)
	validated protocols and devices, continues to be recommended to screen for cases of HT	adults with: [1] high in-office BP to rule out white coat hypertension; and [2] suspected hypertension (including adults with diabetes) to rule out masked hypertension. ABPM is the recommended out-of-office measurement method
2019 JSH [28] (Japanese Society of Hypertension)	Both OBP and HBPM are recommended for HT diagnosis. When a clinic BP-based diagnosis differs from a home BP-based diagnosis, the latter should be predominantly adopted.	HBPM and ABPM are useful for the diagnosis of hypertension, white coat hypertension and masked hypertension, as well as for evaluating the drug effect and its duration
2020 ISH [14], (International Society of Hypertension)	OBP is most commonly the basis for HT diagnosis and follow-up. To confirm the diagnosis of HT 2–3 office visits at 1–4-week intervals (depending on the BP level) are required. The diagnosis of HT might be made on a single visit, if BP is ≥180/110 mmHg and there is evidence of CVD	If possible and available, the diagnosis of HT should be confirmed by out-of-office BP measurement

with clinically significant BP reduction persisting up to 12 months [36]. In consideration of this evidence, it is recommended that implementation of HBPM in hypertension should be accompanied by such co-interventions in all treated hypertensive patients [39].

Since HBPM requires active cooperation by the patient, it may be particularly effective in favourably affecting patients' perceptions of their hypertensive condition, thereby encouraging them to be compliant with lifestyle modifications and prescribed antihypertensive therapy.

2.2. Use of BP telemonitoring

In general, BP values obtained by patients at home are reported in handwritten logbooks which are often incomplete, inaccurate (misreporting), and/or illegible, making interpretation of HBPM values difficult. This may discourage physicians from relying on HBPM data for making clinical decisions. A potentially better solution has been provided more recently by progress in information and communication technologies, which in the last decades have made possible the remote transmission of BP values, measured at home or in a community setting, to the doctor's office or hospital, by means of telehealth applications. The conventional approach to home BP telemonitoring is based on computer-tailored data collection and interventions through the Internet mediated by professional service providers, while more modern solutions are based on mobile health technologies using smartphones and their dedicated applications. Studies in patients with uncontrolled hypertension have provided evidence that telemonitoring-based interventions (i.e. self-BP monitoring with a wireless connection to trasmit BP values to a telemonitoring site) are more effective in reducing BP levels compared to usual care [40]. Of note, a series of interventional studies have provided evidence that telemonitoring associated with patients' self-titration of medication (i.e. medication changes agreed with primary care physicians at baseline, based on the results of self-monitoring, before needing to re-consult) is associated with further reductions in BP values as compared to usual care or even to HBPM without tele-transmission [38,41,42]. Teletransmission of BP values self-measured by patients at home, [41] in particular when combined with education and counselling, has been shown to improve not only patients' adherence to treatment but also doctor-patient relationship. This may help to avoid unnecessary office visits, [43–45], and to achieve more satisfactory hypertension control rates [36,46–49], thus improving cardiovascular prognosis [37,50]. The main disadvantage of conventional HBPT is the high cost of purchasing and maintaining the system, only partly counterbalanced by a reduction in the costs of patients' management compared with usual care. This is of particular importance in the light of the possibility of HBPT being reimbursed by national healthcare systems, which is not currently done in most Countries. Other limitations of HBPT include the need for training and the requirement of a telephone/Internet connection.

2.3. Mobile health: a new approach to HBP telemonitoring

In the era of mobile revolution, the widespread use of smartphone technologies, along with the development of smartphone applications for HBPM and remote transmission (T), have opened new perspectives for HBPT based on the so-called mobile health (mHealth) technologies [51,52]. Main advantages of mHealth technologies include their cost-effectiveness, wide accessibility (large proportion of the population owns a smartphone), and the possibility to link mobile phones and related applications to wearable sensors, with the possibility of multiparametric recording. Although a number of issues, mainly related to the scientific validation of applications developed for mobile healthcare support, still need to be addressed, preliminary data from some clinical studies and a recent meta-analysis have suggested the value of these technologies in improving patients' compliance and adherence to antihypertensive treatment, and in achieving higher BP control rates [53,54] which ultimately might lead to reduce cardiovascular risk. A meta-analysis of randomized controlled trials has shown the efficacy of interactive mobile health (mhealth) interventions in reducing BP levels [54] compared to usual care. Of note, the effects of the mhealth interventions were more evident in patients with inadequate BP control at the time of enrolment [54]. Although blinded prospective randomized clinical trials addressing the role of mHealth strategies for BPT focusing on hard outcomes in the long term are still needed, a few studies addressing the benefits of mobile phone based monitoring of BP control and treatment are currently being conducted [55].

It is of crucial importance, however, that all mobile technologies proposed for use in clinical practice are properly validated in relation to their accuracy in recording the variables of interest.

When considering applications for smartphones, in most cases developed for use in the “fitness” or wellness” world, their content needs to be scientifically validated, and the safety and security of their approach to personal data handling must be guaranteed [51,56]

2.4. Pharmacological regimens considering duration of action of antihypertensive drugs and treatment simplification to improve 24 h BP control and to reduce BP variability

BP fluctuations over a 24h period are characterized by substantial reductions during sleep, a rapid rise upon awakening, and a variable magnitude during the awake state, depending on a person's activities and emotional state [6,7]

While different treatment regimens may have similar BP-lowering effects when assessed at office visits, their impact on daytime and night-time ambulatory BP may vary, also due to the dynamic behaviour of BP during 24 h [57]. The nocturnal BP is now recognized as superior to daytime BP in predicting cardiovascular risk [6]. An increased BP

variability throughout the 24h has been shown to carry prognostic information in addition to that carried by average 24h BP levels, being associated with increased organ damage and incidence of cardiovascular morbidity and mortality [6]. Consequently, the most appropriate agents would be those with a duration of action of 24h or longer, which can be prescribed for once-daily dosing without compromising BP control at the end of the dosing period, thus preserving a physiologic circadian BP pattern and contributing to buffer short term BP fluctuations.

2.4.1. Indices to quantify consistency of BP control over 24h

Indices to assess consistency of BP control throughout the dosing interval, proposed over the years, include trough-to-peak ratio (T/P), smoothness index (SI), and treatment on variability index (TOVI). The 24h trough-to-peak ratio expresses the pharmacological effect of a drug at the end of dosing time (trough) relative to its peak effect. The closer an agent is to a 100% trough-to-peak ratio, the more uniform the 24h coverage and therefore BP control is [58–62]. The Smoothness index (SI) is aimed at providing information on both the degree of 24 h BP reduction and the distribution of such a reduction over the 24h period. SI is obtained by first calculating the average BP values for each hour of the 24 h monitoring period, both before and during treatment. From these values, all hourly changes in BP induced by treatment are obtained, and the average of these hourly values (ΔH) is computed together with its SD, which represents the dispersion of the antihypertensive effect over the 24 hourly values. Finally, the SD is normalized by dividing its value for ΔH, and the inverse of this ratio indicating the degree of 'smoothness' of BP reduction by treatment is termed 'smoothness index'. [64] (See Table 2).

SI overcomes some of the limitations of the trough-to-peak ratio, which focuses only on two narrow time windows over the dosing interval (i.e. peak and trough times). On the contrary, SI provides data on the degree of BP reduction over the entire 24h period, with less variability of results in individual patients [63]. The more effective and constant the therapeutic effect is over the dosing interval (i.e. the greater the average BP reduction and the lower the between-hour differences in the BP reduction induced by treatment), the higher the smoothness index value is [67]. A high SI has been shown to correlate with treatment-induced reduction of left-ventricular mass and with slower progression of carotid artery wall thickness [64,68].

SI data are not widely reported and most studies that have used this index have involved the angiotensin-receptor blockers telmisartan and olmesartan or the ACE inhibitor perindopril, either alone or in combination with amlodipine [69]. A meta-analysis of 11 clinical trials on the effects of antihypertensive treatment on 24h BP found that telmisartan 80 mg and amlodipine 5 mg monotherapies had similar SI values of approximately 1.1, which were superior to those of losartan 50 mg, valsartan 80 mg and 160 mg, and ramipril 10 mg [67]. In a recent pooled analysis of data from 10 randomized-controlled trials with olmesartan, mean SI for SBP was 1.05 for olmesartan monotherapy versus 0.88 for active control monotherapy [66]. In both analyses the indices calculated for combination therapies of the angiotensin II receptor blockers with a diuretic or with a calcium channel blocker (CCB) were significantly higher than the values for monotherapies [66,67]. These findings support the use of fixed-dose combinations of long-acting agents that individually have high SI values as they help to maintain homogeneous 24 h BP control [69]. SI data are also available for the ACE inhibitor perindopril either in combination with amlodipine or with the diuretic indapamide. All of these agents have a long duration of action, and data from two randomized-controlled trials in which 886 subjects were randomized to a single-pill, fixed-dose combination of perindopril/amlodipine 3.5 mg/2.5 mg or to perindopril or irbesartan monotherapy, showed that the combination had a significantly greater SI at 1 month, and therefore a greater reduction of 24h variability [70]. Perindopril has also demonstrated a high SI in combination with indapamide in a 12-month study in which 201 subjects were randomized to this combination (2 mg/0.625 mg) or to atenolol (50 mg) with SI values for SBP of 1.45 for the combination versus 0.98 for atenolol [71].

Treatment On Variability Index (TOVI) is the most recent index for estimating the effect of antihypertensive treatment on BP variability. TOVI indeed reflects the impact of a given treatment both on 24 h mean BP levels and on absolute estimates of 24 h BPV, also accounting for the circadian BP fluctuations (which explain a major part of the variability in the SI), as well as for the dependence of 24-h SD on 24-h mean BP levels. TOVI is estimated as the ratio between mean 24-h BP reduction by treatment and a measure of short-term variability in BP under the same treatment (weighted 24 h Standard Deviation) (Table 2). It therefore differs from the SI, in which the average of the hourly BP reductions and the SD of this average reduction are combined [72]. Finally, an analysis of a large ABPM database, showed that antihypertensive treatment based on a telmisartan/amlodipine combination provided a smoother BP reduction over 24 h (assessed with TOVI and SI) compared to monotherapy [72].

Table 2 summarizes the main features of through-to-peak ratio, smoothness index and treatment on variability index.

2.5. Use of ABPM to assess 24 h BP control by treatment

With the progressive awareness of the importance of 24h BP control, major outcome studies have undertaken ancillary trials using ABPM to further exploit the results of the main study. For example, in the ABPM sub-study of ASCOT-BPLA, patients had repeated ABPM over a median follow-up of 5.5 years. In the amlodipine-perindopril arm,

Table 2
Indices to assess consistency of BP control by treatment.

Index	Meaning	Calculation	Formula
Smoothness Index (SI)	reflects the degree of BP reduction over the entire 24h period	Ratio between the mean of hourly BP reductions (ΔH) and its standard deviation ($SD_{\Delta H}$) [64].	$SI = \frac{\text{Average } \Delta H}{SD\Delta H}$
Through: peak ratio (T/P)	reflects the pharmacological effect of a drug at the end of dosing interval (trough) relative to its peak effect	Ratio between the BP reduction at the end of the between-dose interval (through) and the BP reduction at the time of the maximal drug effect (peak). [65]	$T/P\ ratio = \frac{\Delta\ Trough}{\Delta\ Peak}$
Treatment On Variability Index (TOVI)	reflects the impact of a given treatment both on 24 h mean BP levels and on absolute estimates of 24 h BPV, thus accounting for circadian BP fluctuations, as well as for the dependence of 24-h SD on 24-h mean BP levels	ratio between the mean of 24-hourly BP reductions and the weighted 24-h SD (wSD) assessed under treatment. [66]	$TOVI = \frac{\text{Average } \Delta 24h\ BP}{wSD}$

nighttime systolic BP was lower compared with the atenolol-bendroflumethiazide arm, but daytime systolic BP was higher [57,72]. Patients in both treatment groups who appeared to be well controlled based on clinic BP values were found to be at higher risk of coronary and stroke events if night-time systolic BP was elevated, with a greater risk in the atenolol-bendroflumethiazide arm.

The ABPM substudy of PEARL (PErindopril/Amlodipine Reduction of blood pressure Level), a 3-month observational study, demonstrated a statistically significant reduction in systolic and diastolic within-individual visit-to-visit BP variability, as assessed by the systolic and diastolic BP coefficient of variation, from 10.5/13.5% at baseline to 8.2/11.7% ($P < 0.01$) after 3 months [73]. In addition, an open-label study in general practice which examined the effect on BP of substituting current ineffective antihypertensive treatment with a fixed-dose combination of perindopril/amlodipine in patients with uncontrolled hypertension showed that target BP levels were achieved in the majority of patients at 3 months, with additional beneficial effects on various parameters related to BP variability [74].

2.6. Fixed-dose combinations to simplify therapeutic regimen

Use of fixed-dose combination treatment not only allows to achieve a more powerful BP reduction than monotherapies, but also carries the advantage of simplifying the therapeutic regimen, with a potential beneficial impact on patients' adherence and compliance with prescribed antihypertensive treatment. It is well known that high complexity of antihypertensive regimen (i.e. several medications and a high frequency of administration during the day), is a major barrier for patients' adherence to anti-hypertensive treatment [31]. In a recent study, an inverse and strong relationship was reported between the number of pills that patients were prescribed for the treatment of hypertension and their adherence to treatment [75]. Non-adherence was usually <10% with a single pill, rising to 20% with two pills, and up to 40% with three pills. Very high rates of partial or even complete non-adherence were reported in patients receiving five or more pills [75]. Evidence has indeed been provided that an advantage of long-lasting, single-pill combination therapy is related to the reduction of the burden of antihypertensive and other cardiovascular pills, thus improving quality of life and adherence to prescribed antihypertensive medications [76]. In recognition of this, 2018 ESC/ESH hypertension guidelines have recommended simplifying the therapeutic regimen as a means to improve patients' adherence to treatment. These guidelines, firmly recommended a single-pill combination of two antihypertensive agents as first-line treatment in the majority of patients with hypertension, other than low-risk grade I and the frail elderly [5]. In particular, simplified drug treatment combinations including an ACE inhibitor or an ARB, combined with a CCB and/or a thiazide/thiazide-like diuretic, have been proposed as the core treatment strategy for most patients, with beta-blockers used for specific indications. A large number of antihypertensive agents from these different drug classes are available as single-pill, fixed-dose combinations so that physicians can select a combination of agents tailored to an individual patient's profile. Importantly, some manufacturers also offer flexible dosing with the combination components available as several different dosing options. Thus,contemporary single-pill combination therapy appears to offer a number of potential advantages over monotherapy including a more rapid reduction in BP and greater likelihood of achieving BP targets, reduced pill burden and improved patient's adherence. The efficacy and tolerability profiles of combination therapy have also been evaluated in particular populations such as elderly subjects, in whom achievement of BP control often represents a difficult challenge, mainly due to the adverse effects associated with antihypertensive treatment. In the only randomized, placebo-controlled trial on hypertension management in patients older than 80 years (HYVET study) [77] evidence was provided that compared to placebo, active treatment (sustained release indapamide, ±perindopril), was not only effective in reducing BP levels and cardiovascular outcomes (fatal stroke, all-cause mortality, and heart failure) but also well tolerated and associated with fewer serious adverse events [78]. Results of the HYVET study, however, should be properly interpreted, considering the fact that recruited subjects were "healthy" very elderly individuals with hypertension and no serious co-morbidities.

3. Conclusions

Despite the availability of effective and well-tolerated antihypertensive agents, suboptimal BP control is still the cause of significant morbidity and mortality. Our review of current unmet needs in hypertension management reveals that although we have a range of effective tools for diagnosing hypertension (Table 1), we are not always using them in the most effective way. Office BP values alone fail to identify a significant number of patients with white coat, masked, morning, and night-time hypertension as well as those with excessive 24h BP variability, thus failing from properly characterize their individual risk of cardiovascular events. Greater use of out-of-office BP monitoring needs thus to be made, although further evidence is needed to clarify whether hypertension management based on out-of-office BP does lead to a better outcome than hypertension management guided by OBP. Use of out-of-office BP monitoring, as well as of fixed drug combination treatment, would be particularly useful in high-risk populations such as diabetic or renal patients in whom masked hypertension is a problem often encountered due to lack of night-time dipping. An increased use of long-acting antihypertensive agents and, even better, of their combination, shown to be able to provide a smooth reduction of the 24h BP profile, is also to be recommended. Following the concepts highlighted in the AHA/ACC 2017 and in the ESC/ESH 2018 guidelines, remote monitoring of HBP via modern ICT tools (when properly validated) [51,79], improved team-based care and patient-physician communication, and a simplified single-pill antihypertensive regimen, have the potential to improve treatment adherence and reduce therapeutic inertia while providing rapid and sustained 24h BP control.

Declaration of Competing Interest

None.

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Author contributions

All authors made substantial contributions to the conception and design of the paper, drafting the article and revising it critically for important intellectual content, and gave final approval of the version to be submitted.

Author statement

In relation to our paper IJCJOURNAL-D-20-02559 "Current challenges for hypertension management: from better hypertension diagnosis to improved patients' adherence and blood pressure control" I state that all authors have read and approved submission of this revised manuscript, and this work has not been published and is not being considered for publication elsewhere in whole or part in any language.

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