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REVIEW

Effect of Olmesartan-Based Therapies on Therapeutic Indicators Obtained Through Out-of-Office Blood Pressure

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ABSTRACT

Ambulatory blood pressure (BP) correlates more significantly with hypertension-associated cardiovascular mortality and morbidity than BP obtained in the doctor's office. Assessing ambulatory BP, either through 24-h monitoring or through protocolized self-measurement at home, is essential in diagnosing and monitoring patients with hypertension. Several ambulatory BP-derived indicators are related with cardiovascular prognosis. These include 24-h, daytime and nighttime BP measurements, BP measurements obtained through home self-measurement, dipping status, morning surge, and BP variability. The objective of this article was to review the effect of olmesartan-based antihypertensive therapy on the main risk variables obtained when assessing ambulatory BP.

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INTRODUCTION

Hypertension (HTN) is a key factor in the development of cardiovascular disease. The increase in blood pressure (BP) from optimal levels correlates with coronary heart disease, stroke, heart failure, sudden death, chronic kidney disease, and peripheral arterial disease, which are the leading causes of disease and death in the world. HTN affects 30–40% of the adult population. In addition, BP increases with age so that the prevalence of HTN in the elderly is over 50% [1–3]. In Spain, 33% of adults are hypertensive and the prevalence of HTN in the population over 60 years of age is close to 70% [4]. Antihypertensive treatment is considered to be one of the main achievements in medicine in recent decades, since reducing high BP significantly reduces HTN-related morbidity and mortality [5].

Most of the basic concepts regarding HTN are based on the classical measurement of BP in the

doctor's office. However, the main limitation of this method is that it only offers a momentary BP value that, in addition, is subject to factors that may occasionally change it [6–8]. To optimize assessing true BP values, techniques have been developed to self-measure BP at home, also called home BP monitoring (HBPM) and automated BP measurement over 24 h or ambulatory BP monitoring (ABPM). The BP levels obtained using HBPM [9–14] and those recorded using ABPM [11, 15–21] are more closely correlated with target organ damage and cardiovascular disease than the BP levels obtained in the doctor's office. Ambulatory BP measurement is currently considered a basic indication for diagnosing and monitoring patients with HTN [1, 22].

The objective of this article was to review the studies on the effect of olmesartan-based antihypertensive therapies on the main prognostic indicators related to ambulatory BP.

METHODS

Olmesartan was chosen to perform this review because recent studies analyzing the above-mentioned variables have been developed using this drug. A PubMed search was conducted combining the terms 'olmesartan', 'olmesartan and hydrochlorothiazide', 'olmesartan and amlodipine', 'olmesartan and hydrochlorothiazide and amlodipine', 'home blood pressure measurement', and 'ambulatory blood pressure monitoring'. Furthermore, additional searches were conducted using the terms pertaining to treatments, and 'blood pressure control', 'ambulatory blood pressure control', 'morning surge', 'blood pressure variability', and 'chronotherapy', selecting the studies according to the review objective.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by the author.

CURRENT INDICATIONS FOR AMBULATORY BP MEASUREMENT

As mentioned previously, measuring ambulatory BP is currently considered a basic examination in diagnosing HTN and in assessing the degree of BP control. The recommendations from the British National Institute for Health and Clinical Excellence guidelines establish that either ABPM or HBPM be performed to confirm the HTN diagnosis [22]. The current guidelines from the European Societies of Hypertension and Cardiology define HTN both with the classic in-office figures as well as with ambulatory BP levels [1]. Moreover, ambulatory BP measurement improves the assessment of patients with HTN by determining a series of additional indicators. The current ABPM and HBPM indications from the European Societies of Hypertension and Cardiology are listed in Table 1.

AMBULATORY BP CONTROL MEASURED WITH ABPM

The assessment of ambulatory BP over a 24-h period and the corresponding daytime and nighttime periods is probably the main input for ABPM. As for treated patients, ABPM enables discerning between proper HTN control over 24 h and a lack of true control, not just while at the doctor's office. It is a well-known fact that most patients with HTN need combined treatment with two or more antihypertensive drugs to achieve adequate control, and that

Table 1 Indications for measuring ambulatory blood pressure according to the current guidelines from the European Societies of Hypertension and Cardiology

Indications for HBPM or ABPM
Suspicion of white-coat HTN
Grade I HTN in the office
HTN in individuals without asymptomatic organ damage and at low total CV risk
Suspicion of masked HTN
High normal BP in the office
Normal office BP in individuals with asymptomatic organ damage
Normal office BP in individuals with high total CV risk
Identification of white-coat effect in patients with HTN
Considerable variability of in-office BP during a single visit
Considerable variability of in-office BP over different visits
Suspicion of autonomic, postural, postprandial, siesta- and drug-induced hypotension
HTN or suspected pre-eclampsia in pregnant women
Identification of true and false resistant HTN
Specific indications for ABPM
Marked discordance between in-office BP and home BP
Assessment of dipping status
Suspicion of nighttime HTN or absence of dipping, such as in patients with sleep apnea, chronic kidney disease, or diabetes
Assessment of BP variability

ABPM Ambulatory blood pressure monitoring, *BP* blood pressure, *CV* cardiovascular, *HBPM* home blood pressure monitoring, *HTN* hypertension

Information from Ref. [1]

probably 15–20% of patients need at least three antihypertensive drugs [1]. In the analyses of a national ABPM registry (Spanish ABPM Registry), it has been observed that using a combined antihypertensive treatment is common, especially in cases with high cardiovascular risk, but the ambulatory BP control rate does not reach 50% [23–25]. The data corresponding to the different hypertensive subgroups are presented in Table 2. In low-to-moderate-risk patients without diabetes or kidney disease, a relatively low use of combined treatments was observed, being control rates less than 50%. This figure was probably an expression of therapeutic inertia or nihilism. In higher-risk patients, with diabetes or kidney disease, the therapeutic effort was higher but the control rates were even more unfavorable.

Using combined antihypertensive treatment earlier and a more systematic indication for triple therapy when control is not achieved

Table 2 Prevalence of uncontrolled ambulatory blood pressure in different hypertensive subgroups and usage rates of combination antihypertensive therapies: Data from the Spanish ABPM Registry

Gorostidi et al. [23]: comparison between high-risk and low/moderate-risk subjects with HTN		
	High-risk	**Low/moderate-risk**
N	6534	10,685
Combination of 2 drugs (%)	27.2	19.6
Combination of 3 or more drugs (%)	31.4	13.3
24-h BP ≥130/80 mmHg (%)	76.3	63.9

Gorostidi et al. [24]: comparison between hypertensive subjects with and without diabetes		
	With diabetes	**Without diabetes**
N	12,600	55,445
Combination of 2 drugs	25.1	20.2
Combination of 3 or more drugs	33.8	17.0
24-h BP ≥130/80 mmHg	59.3	55.4

Gorostidi et al. [25]: comparison between hypertensive subjects with and without kidney disease		
	With kidney disease	**Without kidney disease**
N	5693	8689
Combination of 2 drugs (%)	25.9	21.6
Combination of 3 or more drugs (%)	40.2	20.4
24-h BP ≥130/80 mmHg (%)	56.5	53.8

ABPM ambulatory blood pressure monitoring, *BP* blood pressure, *HTN* hypertension

with two drugs might result in improvements in control rates. The most appropriate triple combination has been considered to be one that includes a renin–angiotensin system blocker, a calcium-channel blocker, and a diuretic [1]. As for olmesartan-based combinations, two studies have assessed the degree of control reached in ambulatory BP. In a sub-analysis of the TRINITY trial (Triple therapy with olmesartan medoxomil, amlodipine, and hydrochlorothiazide in hypertensive patients; ClinicalTrials.gov number, NCT00649389) the effect of triple combination therapy was assessed, with doses up to 40 mg of olmesartan, 10 mg of amlodipine, and 25 mg

of hydrochlorothiazide, using ABPM in 440 patients with HTN defined as moderate to severe based on a systolic BP ≥160 mmHg or a diastolic BP ≥100 mmHg. After a 12-week treatment period, 86.5% of patients presented a mean 24-h BP <130/80 mmHg, 79.8% a mean daytime BP <135/85 mmHg, and also 79.8% a mean nighttime BP <120/80 mmHg [26].

In another sub-analysis, in this case the BP-CRUSH study (Blood pressure control in all subgroups with hypertension; ClinicalTrials.gov number, NCT00791258), with a similar design to the previous one and including 243 patients, the degree of ambulatory BP control obtained with the full doses of olmesartan, amlodipine,

and hydrochlorothiazide was 90.5% for mean 24-h BP, 88.4% for daytime BP, and 78.9% for mean nighttime BP, defined as a BP <120/70 mmHg [27]. The characteristics and the basic results of these studies are presented in Table 3.

Logically, in other trials with double combinations of olmesartan and hydrochlorothiazide and of olmesartan and amlodipine, the ambulatory BP control rates were lower although more favorable than those observed in daily practice. In the REZALT study (Efficacy and tolerability of olmesartan medoxomil and azelnidipine combination therapy compared with monotherapy with each agent in Japanese patients with essential hypertension; Japan Pharmaceutical Information Center registration number, JapicCTI-060286), the combination treatment with olmesartan and azelnidipine resulted in a greater decrease in ambulatory BP than with the corresponding monotherapies [28, 29]. In the AZTEC study (AZOR trial evaluating blood pressure reductions and control), with 290 subjects with HTN, 70.9% reached a mean

24-h ambulatory BP <130/80 mmHg with the combination of olmesartan 40 mg and amlodipine 10 mg [30].

In the APEX study (Ambulatory BP monitoring study to evaluate the safety and efficacy of an olmesartan medoxomil- and amlodipine-based treatment regimen in patients with type 2 diabetes and hypertension), 207 patients with type 2 diabetes and HTN received a treatment titrated until reaching the full dose of olmesartan and amlodipine, and 70% of patients reached a mean 24-h daytime BP <130/80 mmHg [31]. The SEVICONTROL-1 (Daytime systolic ambulatory blood pressure with a direct switch between candesartan monotherapy and the fixed-dose combination olmesartan/amlodipine in patients with uncontrolled essential hypertension; ClinicalTrials.gov number, NCT01613209) and SEVICONTROL-2 (Efficacy and safety of a therapy change from candesartan 32 mg to fixed combination of olmesartan 40 mg/amlodipine 10 mg; ClinicalTrials.gov number, NCT01611077)

Table 3 Degree of ambulatory blood pressure control assessed using ambulatory blood pressure monitoring, in studies with olmesartan-based triple combination

Study	N	Patients and methods	Duration	Main outcomes[a]
Izzo et al. [26]	440	Sub-analysis of the TRINITY study. Patients with moderate or severe HTN (systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg) treated with OLM/AML/HCT up to 40/10/25 mg	12 weeks	24-h BP <130/80 mmHg, 86.5%; daytime BP <135/85 mmHg, 79.8%; nighttime BP <120/80 mmHg, 79.8%
Weir et al. [27]	243	Sub-analysis of BP-CRUSH study. Uncontrolled patients with treated with monotherapy OLM/AML/HCT up to 40/10/25 mg	20 weeks	24-h BP <130/80 mmHg, 90.5%; daytime BP <135/85 mmHg, 88.4%; nighttime BP <120/70 mmHg, 78.9%

AML amlodipine, *BP* blood pressure, *BP-CRUSH* blood pressure control in all subgroups with hypertension, *HCT* hydrochlorothiazide, *HTN* hypertension, *OLM* olmesartan, *TRINITY* triple therapy with olmesartan medoxomil, amlodipine, and hydrochlorothiazide in hypertensive patients study

[a] Outcomes obtained with the complete doses

studies, in which 78 and 77 patients, respectively, who were uncontrolled with 32 mg of candesartan, substituted this treatment with the combination of olmesartan 40 mg and amlodipine 10 mg, directly in the SEVICONTROL-1 study and sequentially in the SEVICONTROL-2 study. The daytime ambulatory BP control rates (mean daytime BP <135/85 mmHg) in 12 weeks of treatment were 77.6% and 78.4%, respectively [32, 33].

The fact that the study protocols include strict guidelines on increasing the dose or combining drugs if the clinical BP is not controlled, compared with a possible inertia in routine clinical practice, is one of the factors usually invoked to explain the differences in control rates obtained in clinical trials compared with those observed in care surveys [34].

AMBULATORY BP CONTROL MEASURED WITH HBPM

As mentioned in the introduction, home BP measurements are more useful than in-office measurements for HTN diagnosis, for predicting cardiovascular events and for assessing treatment efficacy. One study, called HONEST (Home blood pressure measurement with olmesartan naive patients to establish standard target blood pressure; Trial registration number, UMIN000002567), with olmesartan-based treatment, was specifically designed to assess the relationships between HBPM with the effects of the therapy. HONEST observed the relationships between the home measurement, clinic measurement, and the incidence of cardiovascular events in 22,373 patients receiving olmesartan-based antihypertensive treatment. Most studies about the relationships between home BP measurements

and cardiovascular prognosis are observations based on initial measurements. The HONEST study will provide data on the prognostic value of home measurements taken during follow-up [35]. In the first publication of results, regarding the short-term efficacy of the olmesartan-based treatment guidelines, it was reported that the percentage of patients who achieved adequate control of clinic systolic BP (systolic BP <140 mmHg) and home systolic BP (systolic BP <135 mmHg), simultaneously, increased from 7.9% to 38.9% after 16 weeks of follow-up [36].

CIRCADIAN RHYTHM AND CHRONOTHERAPY

The relationship between absolute ambulatory BP levels and cardiovascular morbidity and mortality is well established. Of the different periods typically analyzed (24 h, day and night), nighttime BP is the variable that is best correlated with the prognosis. In addition, the relationship between daytime BP and nighttime BP (circadian profile) also predicts HTN-related asymptomatic target organ damage and cardiovascular events [1, 8, 18, 19, 21, 37]. Changes in the normal circadian profile (non-dipper pattern) are very common in hypertensive patients, affecting approximately 50% of cases [38]. There is a close relationship between the non-dipper profile and cardiovascular risk such that in patients at high risk in general or in patients with diabetes and HTN, the prevalence of this change can reach 60% [23, 24].

Chronotherapy in HTN, or administering the hypertensive treatment at a certain time of day, proposes that taking the medication at night has an added beneficial effect on the normal decrease in BP by exercising a favorable action

on the circadian profile with outcomes that even improve morbidity and mortality [39]. However, this therapeutic approach is under debate, as the results of other studies do not corroborate these findings [40]. Regarding olmesartan-based studies, in some, nighttime administration of the drug has been described to result in an added beneficial effect [41, 42] whereas others have not reproduced these results [43, 44]. In the COMPATIBLE study (Comparison of effects of angiotensin II receptor blocker on morning home blood pressure and cardiorenal protection between morning administration and evening administration in hypertensive patients; Trial registration number, UMIN000003238), 218 patients were randomized to take olmesartan in the morning or at night and the reductions in clinic BP, morning home BP, urinary excretion of albumin, and electrocardiographic parameters of left ventricular hypertrophy were similar in patients who received the treatment in the morning or at night [43].

MORNING SURGE IN BP

The increase in BP that is observed when waking and especially when starting daily activity is considered a physiological process. However, there is a controversy about whether or not an excessive morning BP surge may cause a negative prognosis [8]. In this sense, it has been recognized that the antihypertensive treatment that minimizes the morning BP surge, without causing excessive reductions over the rest of the day, has an added beneficial effect.

One of the most studied related variables is the trough-to-peak ratio, considering the peak time as the 2 consecutive hours with the largest reduction in BP in the period between 2 and 8 h

after taking the treatment and the trough time 23 and 24 h after taking the treatment, considering ideal the best proximity to the unit that reflects a homogeneous effect over 24 h. Two recent studies with olmesartan-based treatment have measured this variable. Both in the EXPO study [45, 46] and in Bilo et al. [47], the treatment caused a lasting effect over the 24-h period, with a trough-to-peak ratio greater than 0.6. In the Bilo et al. [47] study, which also assesses this parameter with the olmesartan and amlodipine combinations, a more favorable trough-to-peak ratio was observed in patients who received the combination. Use of long-acting antihypertensive drugs should be of key importance for adequate BP morning surge control. As shown in a recent meta-analysis, losartan was less effective than other angiotensin receptor blockers for controlling 24-h BP [48].

BP VARIABILITY

Although the cardiovascular complications of HTN are essentially related to the absolute BP levels, increased BP variability may have an added deleterious effect. Thus, relationships between cardiovascular morbidity/mortality and very-short-term variability (beat to beat), short term (in a 24-h period), long term (between days), and very long term (between doctor's visits) have been described [49, 50].

There is a close relationship between elevated BP levels, a higher cardiovascular risk, and an increased variability in BP assessed using ABPM [23]. In most of the studies mentioned so far that have assessed this indicator, a reduction in BP variability related to the reduction in absolute BP levels caused by the various treatments was observed. Thus, certain results are of additional interest. In a post hoc analysis

of Japan combined treatment with olmesartan and a calcium-channel blocker versus olmesartan and diuretics randomized efficacy study, in which the patients initially treated with olmesartan were randomized to receive additional treatment with azelnidipine or with hydrochlorothiazide, the patients treated with olmesartan and the calcium-channel blocker presented a higher reduction in day-to-day variability as assessed using HBPM compared to that observed in patients who received olmesartan and the diuretic, despite similar reductions in the absolute home BP levels. In addition, a possible relationship was observed between the reduction in variability and an improvement in a marker of asymptomatic target organ damage, such as aortic rigidity, assessed by measuring carotid–femoral pulse wave velocity [51].

One of the physiopathological changes most closely related to increased BP variability is sympathetic hyperactivity. Accordingly, the results of a sub-analysis of the previously mentioned studies are also of interest. Based on the HONEST data, a higher relative reduction in heart rate was observed in HBPM readings in patients with higher baseline ambulatory systolic BP and heart rate. This tendency was clear in the patient subgroup with chronic kidney disease, in which sympathetic hyperactivity is usually greater. The authors of this study concluded that treatment with olmesartan may have an added beneficial effect on intrarenal circulation in patients with chronic kidney disease and the resulting sympathetic hyperactivity [52].

LIMITATIONS

Most of the studies on the effect of olmesartan and olmesartan-based treatments on variables related to ambulatory BP included in this review are open-label, non-comparative studies. These limitations are recognized in the original publications. Furthermore, the inclusion criteria of this review exclude trials designed the same as those mentioned carried out with other therapeutic alternatives. In this regard, there are studies on the effect of ambulatory BP, mostly with ABPM, with double and triple combinations based on different renin–angiotensin system blockers [53–55] with results in line with those mentioned for olmesartan.

CONCLUSIONS

Assessing ambulatory BP, both for diagnosing as well as for monitoring patients with HTN, and improving the degree of overall HTN control are currently priorities in managing this disease. The results from the studies that have evaluated the effect of olmesartan-based treatments indicate that these have positive effects on the ambulatory BP prognostic indicators such as 24-h BP control, nighttime BP control, BP measured using self-measurement at home, morning surge, and BP variability measured using ABPM or HBPM. It would be desirable to observe whether these benefits translate to reductions in morbidity and mortality in patients with HTN.

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Compliance with ethics guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by the author.

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