IDENTIFYING MASKED UNCONTROLLED HYPERTENSION IN THE COMMUNITY PHARMACY SETTING

RUNNING HEAD: Factors associated with masked uncontrolled hypertension.

Authors, on behalf of the MEPAFAR study workgroup:

D. Sabater-Hernández. PharmD, PhD. Chancellor's Postdoctoral Research Fellow; Graduate School of Health, University of Technology, Sydney, Australia. Fellow; Academic Centre in Pharmaceutical Care, University of Granada, Spain. Email: daniel.sabaterhernandez@uts.edu.au

J. Sendra-Lillo. PharmD, PhD. Pharmacist. Community pharmacy Angel Sendra Ortola. Fellow; Academic Centre in Pharmaceutical Care, University of Granada, Spain. Email: jose_sendra_lillo@yahoo.es

J.J. Jiménez-Monleón. MD, PhD. Associate Professor; Faculty of Medicine, University of Granada, Spain. Email: jjmonleon@ugr.es

S.I. Benrimoj. PharmD, PhD. Head of School; Graduate School of Health, University of Technology, Sydney, Australia. Email: shalom.benrimoj@uts.edu.au

D. Durks. BPharm. Student; Graduate School of Health, University of Technology, Sydney, Australia. Email: desire.durks@uts.edu.au

F. Martínez-Martínez. PharmD, PhD. Associate Professor; Faculty of Pharmacy, University of Granada, Spain. Director; Academic Centre in Pharmaceutical Care, University of Granada, Spain. Email: fmartin@ugr.es

A. de la Sierra. MD, PhD. Head of department; Department of Internal Medicine, Hospital Mutua Terrassa, Spain. Associate Professor; Faculty of Medicine, University of Barcelona, Spain. Email: adelasierra@mutuaterrassa.cat

List of the MEPAFAR study workgroup: Hernández-Peña N, Sabater-Díaz JM, Artiles-Campelo A, Jorge-Rodríguez ME, García-Morales MF, García-Rodríguez AR, Merino-Barber L, Santana-Perez F, Díaz-Merino N, Artiles-Ruano ME, Contardi-Lista AM.

Corresponding author: Daniel Sabater-Hernández

Address: Graduate School of Health, University of Technology Sydney. Level 13, 15 Broadway, Ultimo NSW 2007 (PO Box 123). Phone: +61 2 9514 7201. Email: Daniel.SabaterHernandez@uts.edu.au

Abstract

Background. Masked uncontrolled hypertension (MUCH) is associated with an increased cardiovascular risk. This condition is frequent in the community pharmacy (CP-MUCH), but there is no evidence on the factors associated to its presence in that setting. The aim of this analysis was to explore those factors. **Methods.** A sample of 98 treated hypertensive patients from the MEPAFAR study, with normal community pharmacy blood pressure (CPBP <135/85 mmHg), were analyzed. BP was also measured at home (4 days) and monitored for 24-hour. CP-MUCH was identified when either ambulatory (daytime) or home BP averages were ≥135/85 mmHg. A multivariate logistic regression analysis was performed to identify the factors associated with CP-MUCH. **Results.** The prevalence CP-MUCH tends to be higher as systolic and diastolic CPBP increases, reaching 47% in patients with both systolic CPBP ≥123 mmHg and diastolic CPBP ≥79 mmHg. The multivariate regression analysis revealed only systolic CPBP as an independent factor of CP-MUCH [≥123 mmHg: OR=16.46 (p=0.012); from 115 to 122.9 mmHg: OR=10.74 (p=0.036); systolic CPBP <115 mmHg as the reference]. **Conclusion.** Further assessment, using ambulatory and/or home BP monitoring, is recommended in patients with normal CPBP, but systolic CPBP ≥115 mmHg. A more feasible approach would be evaluating patients with both systolic CPBP ≥123 mmHg and diastolic CPBP ≥79 mmHg.

Keywords: Hypertension; Masked Hypertension; Risk Factors; Community Pharmacy Services.

Introduction

Masked uncontrolled hypertension (MUCH) is defined in those treated hypertensive patients who have elevated ambulatory (ABP) or home blood pressure (HBP) despite normal physician office measurements[1]. This condition is found in 22% of treated patients and has been associated with an increased cardiovascular risk[2]. This higher risk may be explained by the fact that ABP and HBP have been shown to be stronger predictors of target organ damage and cardiovascular events than blood pressure measured in a physician's office (BP)[3,4].

MUCH could remain undetected if only office BP readings are available for evaluation. As a consequence, if normal BP figures are measured in the physician's office, the necessary adjustments in treatment may not be made and the underlying risk associated with elevated ABP or HBP would therefore not be well managed. As measuring out-of-office BP in all normotensive individuals is not a feasible or efficient strategy in daily clinical practice, several studies have been carried out to identify the factors associated with the presence of MUCH[5-9]. By considering these factors and identifying patients who are more likely to have MUCH, a further assessment, using ABP or HBP monitoring, could be recommended.

MUCH has also been identified as a relatively frequent condition in the community pharmacy (CP-MUCH)[10,11]. Particularly in this case, if normal BP figures are measured in the community pharmacy, pharmacists would not refer patients to a physician, and again, the necessary changes in treatment would not be made. Given that CP-MUCH could influence both decision-making

processes and health outcomes, the presence of this condition should be carefully investigated when pharmacists deliver pharmaceutical care services to treated hypertensive patients.

To our knowledge, there are no reports in the literature on the factors associated with CP-MUCH. As a consequence, community pharmacists do not have guidelines which would allow them to better identify patients who are likely to present with CP-MUCH. In light the prevalence of CP-MUCH and given its clinical implications, a subgroup analysis of patients with normal community pharmacy BP (CPBP) who were included in the *MEPAFAR study*[11] was carried out to explore the factors associated with CP-MUCH.

Methods

The *MEdida de la Presión Arterial en FARmacia (MEPAFAR) study* was a cross-sectional study, conducted from June 2008 to June 2009 in 8 Spanish community pharmacies. The main aim of the study was to assess the agreement between CPBP, daytime ABP, and HBP in treated hypertensive patients[11] and so, the capacity of the CPBP measurement method to evaluate the effectiveness of antihypertensive treatment. The protocol of the MEPAFAR study was assessed and approved by the Research Ethics Committee of the University of Granada (Spain).

BP measurements methods have been comprehensively described in previous publications[11,12]. Briefly, CPBP was measured at 4 visits, by the same pharmacist at each pharmacy, over a 4-week period. At each visit, 3 BP measurements were taken (2-3 minutes apart) on the control arm (arm on which CPBP was higher on the first visit). Patients' visits to the pharmacy were

scheduled at the same time for all 4 time points (± 1 hour). Mean CPBP was calculated discarding the data from the first visit and the first measurement from each visit. For the purpose of this sub-analysis, normal CPBP was defined by systolic BP (SBP) <135 mmHg and diastolic BP (DBP) <85 mmHg.

At home, patients monitored their BP over 4 consecutive working days, taking 3 measurements in the morning (2 minutes apart, 6am to 9am) and 3 measurements in the evening (6pm to 9pm) on the non-dominant arm. HBP readings were stored in the device's memory. Mean HBP was calculated, discarding values obtained on the first day and using the first and second measure from each morning and each evening. Normal HBP was defined by SBP <135 mmHg and DBP <85 mmHg. The clinically validated OMRON M10-IT automatic electronic device (Omron Corp, Tokyo, Japan)[13] was used both at home and in the community pharmacy.

ABPM was performed on a working day (24 hours), using the non-dominant arm. Measurements were taken every 20minutes (7am to 10pm) or 30 minutes (10pm to 7am). The clinically validated Spacelabs Medical 90207-5Q monitor (Spacelabs Inc., Redmond, WA) was used[14]. Average daytime ABP was calculated according to a sleep diary kept by each patient. Normal daytime ABP was defined by SBP <135 mmHg and DBP <85 mmHg.

Based on recent acknowledged definitions[15,16], CP-MUCH was defined when an average CPBP (SBP/DBP) of <135/85 mmHg was combined with one or both of the following: average daytime ABP ≥135/85 mmHg and/or average HBP≥135/85 mmHg.

To characterize the study sample, the following variables were collected: age, gender, smoking status, body mass index (BMI), number of antihypertensive drugs used, adherence to antihypertensive drugs (Morisky-Green test[17]), history of previous cardiovascular disease (stroke, myocardial infarction, angina, or peripheral artery disease), and presence of diabetes or dyslipidemia (documented diagnosis or previously prescribed drug treatment).

Statistical analysis. SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical calculations. Mean and standard deviation (SD) were used to summarize quantitative variables. Qualitative variables were described using frequencies and percentages. To compare the quantitative variables, Student's t test for independent samples was used. Differences between CPBP, HBP, and daytime ABP were assessed by repeated measures analysis of variance, applying the Bonferroni correction. Chi-square and Fisher's exact tests were performed for comparisons of proportions.

To identify the independent factors associated with CP-MUCH a multivariate logistic regression analysis was used. As candidate independent variables for the multivariate models, CPBP (SBP and DBP) and all the variables collected to characterize the study sample were considered. Univariate logistic regression was used to select the variables that were finally entered in the multivariate models (p value <0.2). A priori, quantitative independent variables (i.e., SBP, DBP, age and BMI) were entered into the model in their original form. However, none of them showed a linear relationship with the dependent variable, when linearity was checked. Due to this fact, these quantitative variables were converted into categorical variables based on their tertiles (i.e., each variable was stratified in 3 groups with similar number of individuals). A second

multivariate logistic model was constructed using CP-MUCH, defined by daytime ABP only, as the dependent variable. The goodness-of-fit of the models was assessed using the Hosmer-Lemeshow test (the model was considered acceptable if the test was not statistically significant). A p-value <0.05 was considered statistically significant.

Results

The final sample of the *MEPAFAR study* comprised 169 treated hypertensive patients; 98 of whom had CPBP <135/85 mmHg. This sub-group of 98 was the subject of the present analysis. The general characteristics of the sample are shown in table 1.

CP-MUCH was found in 24 (24.5%) individuals: 11 of whom had uncontrolled HBP only; 8 had uncontrolled daytime BP only; and 5 had both home and daytime uncontrolled BP. Patients with CP-MUCH presented significantly higher CPBP, HBP and ABP than those without the condition; however, none of the mean BP values were above the threshold limits (table 1). Among patients with CP-MUCH, those with both home and daytime uncontrolled BP (n=5) presented the highest SBP figures [128.6 (SD: 6.6) at the pharmacy, 140.0 (SD: 6.4) mmHg at home, and 139.6 (SD: 3.4) mmHg by ambulatory monitoring] (figure 1).

As shown in table 2 and figure 2, the proportion of individuals with CP-MUCH tends to be higher as systolic and diastolic CPBP increases; for example, the prevalence of CP-MUCH reached 47% (7 out of 15) in patients with systolic CPBP ≥123 mmHg and diastolic CPBP ≥79 mmHg. Based on the univariate regression analysis, age, diabetes, and both systolic and diastolic CPBP were

8

selected as factors to be entered into the multivariate model (table 2). The multivariate regression analysis revealed systolic CPBP ≥115 mmHg as an independent factor of CP-MUCH [from 115 to 122.9 mmHg: OR=10.74 (p=0.036); ≥123 mmHg: OR=16.46 (p=0.012); systolic CPBP <115 mmHg as the reference]. When only daytime ABP was used to identify CP-MUCH (n=13), again, only systolic CPBP was found to be associated [≥123 mmHg: OR=10.85 (p=0.036); systolic CPBP <115 mmHg as the reference].

Discussion

Measurement of BP in community pharmacies is a widespread practice that is recommended by several hypertension societies[18-20]. Nevertheless, some caution should be exercised when considering and using this method; specifically, when normal figures are obtained, CPBP readings might encourage erroneous conclusions about hypertension control in some cases. In fact, in this study, CP-MUCH was identified in a quarter of the patients with normal CPBP. Ideally, ABPM and/or HBPM would be recommended in all patients with normal CPBP; however, this is not feasible or achievable in practice. In light of this, our results might assist community pharmacists to identify individuals who are more likely to present CP-MUCH and, thus, prioritize the use of the out-of-pharmacy BP methods among treated hypertensive patients with normal CPBP.

Based on the results of the multivariate analysis, CP-MUCH was associated with systolic CPBP and should be investigated when systolic figures ≥115 mmHg are obtained. However, due to the low BP cut-off point, this recommendation still encourages a wide use of ABPM and/or HBPM that might not be achievable in some cases (for example, a patient's lack of willingness to

monitor BP). Additional results of this study allow identification of certain circumstances in which either the prevalence of CP-MUCH or the relevance of the situation might be greater. When CP-MUCH was defined by means of ABPM only, the multivariate analysis revealed that individuals with systolic CPBP ≥123 mmHg are more likely to present CP-MUCH. This is particularly noteworthy when it is considered that ABPM is the reference method in the management of hypertension. In addition, although diastolic CPBP was not associated with CP-MUCH, the prevalence of CP-MUCH increased (across any systolic BP strata) as diastolic CPBP was closer to the upper-normal limits (≥79 mmHg; figure 2). Overall, HBP and ABP figures were not remarkably elevated in patients with CP-MUCH (table 1, figure 1). Only individuals with both home and daytime uncontrolled BP revealed high SBP figures. Interestingly, 4 out of these 5 individuals had systolic CPBP ≥123 mmHg. Based on these observations taken together, community pharmacists would be encouraged to further assess BP control (using ABPM and/or HBPM) when systolic CPBP ≥123 mmHg and diastolic CPBP ≥79 mmHg. From a practical perspective, this might represent a more feasible approach than considering all the individuals with systolic CPBP ≥115 mmHg.

This study provides original evidence of the factors associated with CP-MUCH, which, at first instance, should not be assumed to be the same condition as presents in the physician office. This statement is based the results of the *Palmera study*[10] in which CPBP and physician office BP inversely classified BP control in 34.3% of patients (kappa coefficient for the agreement between methods: 0.35). These results suggest that individuals with CP-MUCH would be unlikely to be the same individuals as those presenting with MUCH in the

physician office. Thus, factors associated with MUCH should be independently studied in both of these settings. As a reasonable starting point, our primary analysis included and checked many factors that have been previously associated with MUCH in the physician office: gender[5-7], age[5-7], smoking status[6], clinic BP[5-9] (instead of CPBP), BMI[5,8], number of antihypertensive drugs taken[8,9] and diabetes[5]. In our opinion, other potential factors[21] might be taken into account in the future, considering also undiagnosed patients and large samples. Another interesting subject to be addressed by future research would be the reproducibility of CP-MUCH. Nonetheless, while additional evidence is generated in other studies, we believe our results will be useful for improving the assessment of BP in treated hypertensive patients and for detecting CP-MUCH.

According to recent hypertension guidelines[15,16], we used a single definition of CP-MUCH, combining the results of both HBP and ABP monitoring. On the one hand, this represents a more conservative approach, since, theoretically, patients with either elevated HBP or elevated daytime ABP require further evaluation. On the other hand, most patients with CP-MUCH had only one out-of-pharmacy BP elevation, thus revealing that both methods are complimentary and that incomplete information is obtained when one is used in isolation. It should be noted that all patients included in this analysis were adherent to the HBPM protocol (4 days; 3 measurements in the morning and 3 in the evening), so the minimum number of HBP measures established by international guidelines for assessing hypertension was reached[22,23].

The results of this study are constrained by the procedures used for measuring BP at the community pharmacy. The measurement approach is supported by

the Spanish Society of Hypertension[19] and was initially established based on guidelines for BP measurement in the clinic[24], which recommend taking repeated BP measures per visit over at least 2 to 3 visits. In addition, based on previous results of this study[12,25], the data from the first pharmacy visit and the first measurement from each visit were discarded in order to minimize the white-coat effect. Thus, it seemed reasonable to use the same threshold limits for HBP and daytime ABP. This protocol for measuring CPBP follows the guidelines and, thus, meets the standards of quality care. Moreover, in our opinion, it is simple and might be easily implemented in practice. Finally, it should be noted that measuring BP by community pharmacists can be used as a first step in assessing BP control in hypertensive treated patients who are not willing or capable to monitor either HBP or ABP[26]. Then, based on measured CPBP, pharmacist may recommend to some patients a further BP assessment using ABPM and/or HBPM[19,23,27].

In conclusion, CP-MUCH, which affected a quarter of the patients in this study, was only associated with systolic CPBP. Further assessment, using ABPM and/or HBPM, is recommended in treated hypertensive patients with controlled CPBP, but who have systolic figures ≥115 mmHg. A more feasible approach however would be to evaluate patients with both systolic CPBP ≥123 mmHg and diastolic CPBP ≥79 mmHg. These results may assist in promoting better management of hypertension from the community pharmacy.

Acknowledgments

References

1. Banegas JR, Ruilope LM, de la Sierra A, de la Cruz JJ, Gorostidi M, Segura J, et al. High prevalence of masked uncontrolled hypertension in people with treated hypertension. *Eur Heart J* Epub 2014 Feb 3.

2. Verberk WJ, Kessels AG, de Leeuw PW. Prevalence, causes, and consequences of masked hypertension: a meta-analysis. *Am J Hypertens* 2008; 21(9): 969-75.

3. Fagard RH, Van Den Broeke C, De Cort P. Prognostic significance of blood pressure measured in the office, at home and during ambulatory monitoring in older patients in general practice. *J Hum Hypertens* 2005; 19(10): 801-7.

4. Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation* 2005; 111(14): 1777-83.

5. Andalib A, Akhtari S, Rigal R, Curnew G, Leclerc JM, Vaillancourt M, et al. Determinants of masked hypertension in hypertensive patients treated in a primary care setting. *Intern Med J* 2012; 42(3): 260-6.

6. Kim SK, Bae JH, Nah DY, Lee DW, Hwang TY, Lee KS. Frequency and related factors of masked hypertension at a worksite in Korea. *J Prev Med Public Health* 2011; 44(3): 131-9.

7. Mallion JM, Clerson P, Bobrie G, Genes N, Vaisse B, Chatellier G. Predictive factors for masked hypertension within a population of controlled hypertensives. *J Hypertens* 2006; 24(12): 2365-70.

8. Obara T, Ohkubo T, Funahashi J, Kikuya M, Asayama K, Metoki H, et al. Isolated uncontrolled hypertension at home and in the office among treated hypertensive patients from the J-HOME study. *J Hypertens* 2005; 23(9): 1653-60.

9. Park SJ, Park JB, Choi DJ, Youn HJ, Park CG, Ahn YK, et al. Detection of masked hypertension and the 'mask effect' in patients with well-controlled office blood pressure. *Circ J* 2011; 75(2): 357-65.

10. Sendra-Lillo J, Sabater-Hernández D, Sendra-Ortolá A, Martínez-Martínez F. Agreement between community pharmacy, physician's office, and home blood pressure measurement methods: The Palmera Study. *Am J Hypertens* 2012; 25(3): 290-6.

11. Sabater-Hernández D, de la Sierra A, Sánchez-Villegas P, Santana-Pérez FM, Merino-Barber L, Faus MJ. Agreement between community pharmacy, ambulatory and home blood pressure measurement methods to assess the effectiveness of antihypertensive treatment. The MEPAFAR study. *J Clin Hypertens (Greenwich)* 2012; 14(4): 236-44.

12. Sabater-Hernández D, de la Sierra A, Sánchez-Villegas P, Baena MI, Amariles P, Faus MJ. Magnitude of the white-coat effect in the community pharmacy setting: The MEPAFAR Study. *Am J Hypertens* 2011; 24(8): 887-92.

13. Altunkan S, Ilman N, Kayaturk N, Altunkan E. Validation of the Omron M6 (HEM-7001-E) upper-arm blood pressure measuring device according to the International Protocol in adults and obese adults. *Blood Press Monit* 2007; 12(4): 219-25.

14. O'Brien E, Mee F, Atkins N, O'Malley K. Accuracy of the SpaceLabs 90207 determined by the British Hypertension Society protocol. *J Hypertens* 1991; 9(6): 573-4.

15. Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, et al. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. *J Hypertens* 2014; 32(7): 1359-66.

16. O'Brien E, Parati G, Stergiou G, Asmar R, Beilin L, Bilo G, et al. European society of hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens* 2013; 31(9): 1731-68.

17. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986; 24(1): 67-74.

18. Chan AHW, Campbell NR, Lewanczuk RZ, Semchuk W, Thompson A, Tsuyuki R. ; the Canadian Hypertension Education Program Implementation Task Force. 2008 Canadian Hypertension Education Program Guidelines for the management of hypertension by pharmacists. *Can Pharm J* 2008; 141(6): 327-31.

19. Sabater-Hernández D, de la Sierra A, Bellver-Monzó O, Divisón JA, Gorostidi M, Perseguer-Torregosa Z, et al. Action guide for community

pharmacist in patients with hypertension and cardiovascular risk. Consensus document (condensed version). *Hipertens riesgo vasc* 2011; 28(5-6): 169-81.

20. Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, et al. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ* 2004; 328(7440): 634-40.

21. Yano Y, Bakris GL. Recognition and management of masked hypertension: a review and novel approach. *Journal of the American Society of Hypertension : JASH* 2013; 7(3): 244-52.

22. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31(7): 1281-357.

23. Parati G, Stergiou GS, Asmar R, Bilo G, de Leeuw P, Imai Y, et al. European Society of Hypertension practice guidelines for home blood pressure monitoring. *J Hum Hypertens* 2010; 24(12): 779-85.

24. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; 25(6): 1105-87.

25. Sabater-Hernández D, Sánchez-Villegas P, Lacampa P, Artiles-Campelo A, Jorge-Rodriguez ME, Faus MJ. Evaluation of the hypertensive state in treated patients: selection of appropriate blood pressure measurements per visit to the community pharmacy. *Blood Press Monit* 2011; 16(3): 103-10.

26. Sabater-Hernandez D, Sendra-Lillo J, Faus MJ, Martinez-Martinez F, de la Sierra A. Usefulness of blood pressure measurement by community pharmacists in the management of hypertension. *J Manag Care Pharm* 2012; 18(6): 453-6.

27. James K, Dolan E, O'Brien E. Making ambulatory blood pressure monitoring accessible in pharmacies. *Blood Press Monit* 2014; 19(3): 134-9.
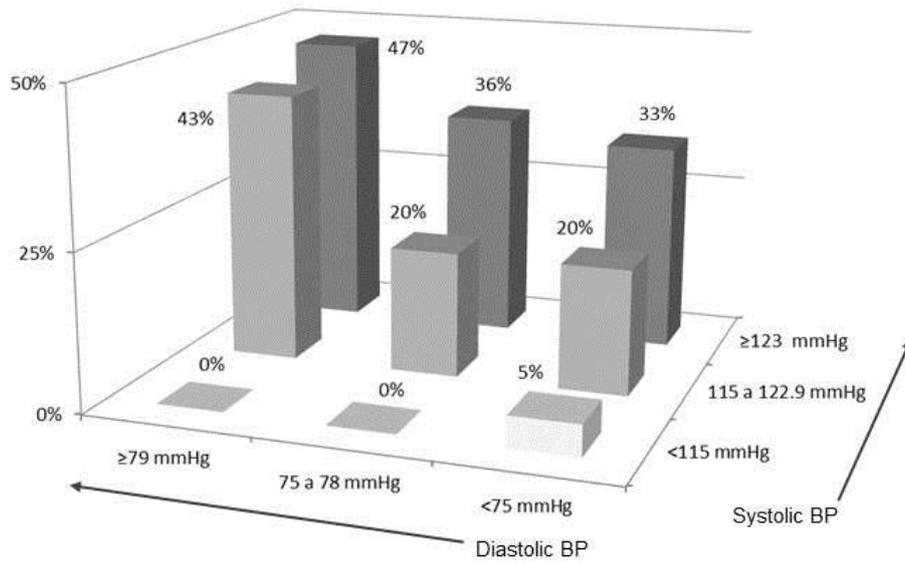
Figure 1. Average blood pressure figures in patients with CP-MUCH.
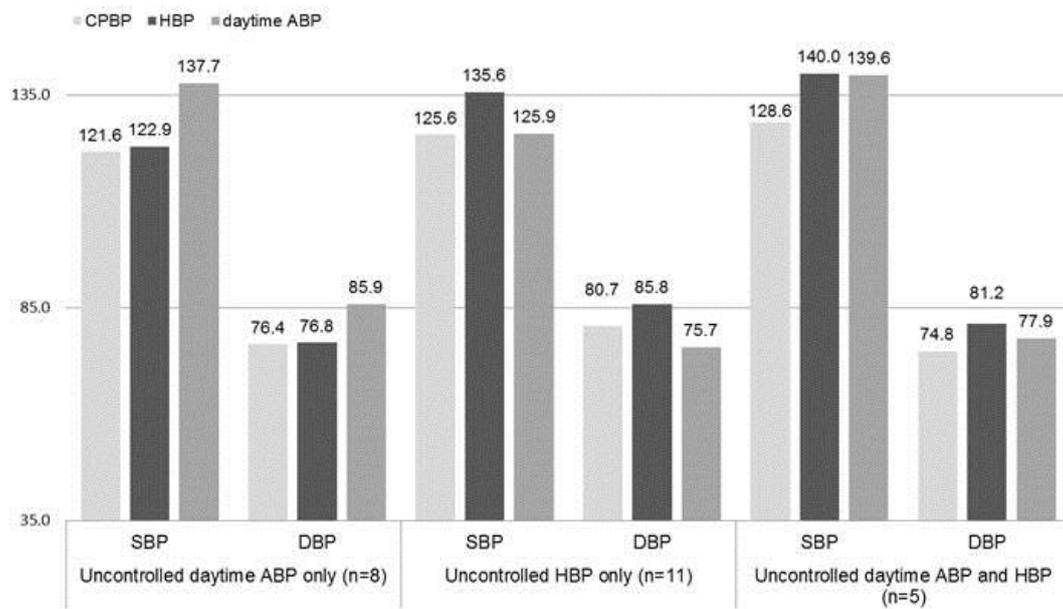
Legend:

ABP: ambulatory blood pressure; CPBP: community pharmacy blood pressure; DBP: diastolic blood pressure; HBP: home blood pressure; SBP: systolic blood pressure.

FIGURE 2. Prevalence of CP-MUCH across blood pressure strata in the

community pharmacy

Legend:

BP: blood pressure.