Factors related to blood pressure control in a prospective cohort of hypertensive outpatients

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ABSTRACT. Previous studies have reported a controversial relationship between inadequate blood pressure control and predictor variables. Current prospective cohort study analyzes the interference of age, gender, diabetes and medication adherence in the control of blood pressure of hypertensive outpatients. Patients were interviewed under blind conditions to determine medication adherence, and clinical variables assessment were standardized. Univariate analysis of variance identified the variables correlated to blood pressure control at the end of the follow-up period. Missing data were excluded from analysis. After adjusting for confounders with univariate analysis, the association between the outcome (BP control rate) with significant factors and the calculated adjusted odds ratios (OR) and their 95% CI was analyzed by logistic regression. No interference by age or medication adherence in blood pressure control was reported. In fact, the higher the number of medications in use, the greater were the chances of having blood pressure control in disorder. Females are associated with a 3.1 increase in odds ratio of poor blood pressure control. Compared with non-diabetic hypertensive patients, hypertensive diabetic ones had a lower chance of poor blood pressure control.

Keywords: patient compliance. medication adherence. hypertension. family health strategy.

Fatores relacionados ao controle da pressão arterial em coorte prospectiva de pacientes hipertensos ambulatoriais

RESUMO. Estudos anteriores encontraram relações controversas entre o inadequado controle da pressão arterial e variáveis preditoras. Nesta coorte prospectiva, objetivamos analisar a interferência da idade, do gênero, da presença de diabetes e da adesão à medicação no controle da pressão arterial em pacientes hipertensos ambulatoriais. Os pacientes foram entrevistados sob condições de cegamento dos avaliadores na mensuração da adesão à medicação, e a metodologia de avaliação das variáveis clínicas foi padronizada. Uma análise univariada identificou quais variáveis correlacionaram-se com o controle da pressão arterial ao final do período de seguimento. Dados faltantes foram excluídos da análise. Após ajuste para variáveis de confusão por meio da análise univariada, analisamos as associações entre o desfecho (controle da pressão arterial) e variáveis preditoras, e calculamos o odds ratio ajustado e seu intervalo de confiança de 95%, utilizando regressão logística. Não encontramos interferência da idade ou aderência aos medicamentos no controle tensional. Constatamos que, quanto maior o número de medicamentos em uso, maiores as chances de apresentar controle tensional fora das metas. O gênero feminino associou-se com o aumento de 3,1 vezes na chance de mau controle da pressão arterial. Comparados com pacientes hipertensos não diabéticos, os hipertensos diabéticos tiveram menores chances de apresentar mau controle tensional.


Introduction

Despite progress in the quality of health care and availability of antihypertensive drugs in recent decades, blood pressure control rates remain insufficient. Inadequate blood pressure (BP) control rates have ranged between 30.0 and 53.9% among people followed up in basic health units (Pinho & Pierin, 2013). Previous cross-sectional and cohort studies registered a controversial relationship between inadequate BP control and predictor variables. In a large German cross-sectional study with over 50,000 outpatients, uncontrolled BP was associated with aging, obesity and male gender (Labeit et al., 2012). In another cross-sectional study, inadequate BP control was associated to multimorbidity, high number of medications and male gender (Sarkar et al., 2015).
In the TAPAS study, the authors found the anthropometric variable (weight gain), high baseline LDL cholesterol and no reduction in fasting glucose as predictors for failing to maintain BP goals (Suarez, Galgo, Mantilla, Leal, & Escobar, 2014). Diabetes, congestive heart failure and chronic kidney disease were predictors of uncontrolled BP in another retrospective study (Rowan, Turner, Shah, & Spaeder, 2014). Contrastingly, diabetes and baseline systolic blood pressure (SBP) were positively associated with SBP improvement, while age and polypharmacy were negatively associated with the same outcome (Aydogan et al., 2015).

Current study analyzes the interference of age, gender, diabetes and medication adherence in controlling blood pressure in a prospective cohort of hypertensive outpatients.

Material and methods

Current longitudinal cohort study involved a target population comprising adult outpatients with essential hypertension (EH), receiving pharmacologic treatment, who lived in the coverage area of a Family Health Strategy (an assistance health model for the reorganization of primary health care at a nationwide level in Brazil) in a town with nearly 17,000 inhabitants.

Sample size was calculated at a 95% confidence level, 80% power, ratio of unexposed/exposed (medication adherence) of 4, unexposed percentage with 40% outcome and exposed percentage with a 86% outcome (Taira et al., 2007). A sample size of 190 EH patients were computed. A 20% margin was added for possible losses or refusals, forming a sample of 228 individuals.

Inclusion criteria comprised patients (a) aged 18 years and older; (b) with confirmed diagnosis of EH according to the VI Brazilian Guidelines in Arterial Hypertension (Sociedade Brasileira de Cardiologia, Sociedade Brasileira de Hipertensão, & Sociedade Brasileira de Nefrologia, 2010) and have been using antihypertensive medications for at least three months; (c) with no current use or previous history of alcoholism, according to the Diagnostic and Statistic Manual of Mental Disorders (DSM-IV) (Pierucci-Lagha et al., 2007); (d) with no communication or intellectual deficits that might interfere in the comprehension of the informed consent form and interview (the Seven-Item Measure Treatment Adherence scale). Patients were excluded if a diagnosis of secondary hypertension was suspected or confirmed, if they were pregnant and if they had been included in pharmacologic intervention clinical trials.

Written consent was obtained during enrollment. The study was approved by the local institutional Committee for Ethics, protocol number 11540313.6.0000.5502. Data were collected between March 2011 and December 2013.

On admission, patients were interviewed under blind conditions by a researcher without access to medical history, but who had previous experience in anthropometric measurements and clinical evaluation. The seven-item Measure Treatment Adherence scale (MTA) (Delgado & Lima, 2001) was applied to establish medication adherence. MTA consists of seven items that assess an individual’s behavior on everyday use of drugs. The score is obtained by means of an ordinal six-point scale that varies from 1 (corresponding to ‘always’ [lowest adherence]) to 6 (corresponding to ‘never’ [highest adherence]). The level of adhesion is obtained by summing the rates of each item and dividing the product by the number of items. Higher rates correspond to higher adherence to medication. The analysis of MTA answers was described elsewhere (Gimenes, Zanetti, & Haas, 2009).

Self-reports of cardiovascular disease (CVD) at baseline were validated according to review of medical records and results of complementary exams. CVD was defined as previous history of: myocardial infarction, stroke, congestive heart failure, angina, claudication or transient ischemic attack. Medication in current use on admission was confirmed through a review of pharmacy records. Polypharmacy is defined as the use of five or more medications.

Patients were categorized as having Type 2 Diabetes Mellitus (T2DM) at admission if they reported use of oral hypoglycemic medications or insulin; occurrence of new cases of T2DM during the study period were diagnosed using valid criteria (López-Jaramillo et al., 2013).

Smoking was categorized as current use, previous use (the patient discontinued the use of tobacco for more than three months, without relapse) and lack of use. Patients were considered sedentary if they did not meet the criteria of regular physical activity (Sociedade Brasileira de Cardiologia et al., 2010).

BP and anthropometric data measurements were standardized, and all staff involved in the research adopted the same criteria (Sociedade Brasileira de Cardiologia et al., 2010). Hypertensive patients were considered as having properly controlled BP when systolic BP was < 140 mmHg and diastolic BP was < 90 mmHg. In hypertensive and diabetic patients, goals of BP control were 130 x 80 mmHg. All patients included in the study attended to (at least)
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three clinical routine visits. Mean SBP and DBP (BP control) were calculated during these visits and a categorical variable was computed with the information (BP control) according to goals for EH or EH and T2DM.

Weight (in kilograms) was calculated with a Filizola® equipment (150-kg capacity, 100 g sensitivity scale), with patients wearing light clothing and no shoes; height (in centimeters) by measured with a fixed stadiometer; waist circumference (WC), in centimeters, was calculated with a tape measure, at the midpoint between the last rib and the iliac crest, during expiration. Body Mass Index (BMI) was obtained by the ratio between body weight and the square of the height, following classification of the World Health Organization (WHO, 1995).

Laboratory workup results of glycosylated hemoglobin (HbA1c) were performed in the same laboratory featuring quality control certified by PELM (Excellence Program for Medical Laboratories), PNCQ (National Program for Quality Control) and CDC (Centers for Disease Control and Prevention). HbA1c serum levels were altered if ≥ 7%.

Shapiro-Wilk test verified the normal distribution of variables. Descriptive statistics comprised mean ± standard deviation or median (25-75th percentiles) and frequency/proportion of observations. Baseline characteristics were compared between age category (< 65 years /65 years and more), gender, presence/absence of T2DM, medication adherence/non-adherence and use (or not) of polypharmacy, using parametric and non-parametric tests. Univariate analysis of variance identified the variables correlated to blood pressure control at the end of the follow-up period.

Missing data were excluded from analysis. After adjustment for confounders by univariate analysis, the associations between the outcome (BP control rate) with significant factors were analyzed, and adjusted odds ratios (OR) and their 95% CI were calculated by logistic regression. Rate sp ≤ 0.05 indicated statistical significance. All data analyses were conducted with SPSS 19.0®.

**Results**

Two hundred and thirty-two patients were enrolled in baseline but only 213 comprised the cohort till the end of follow up (Figure 1). Table 1 shows baseline characteristics of the cohort sample.

### Table 1. Main clinical characteristics of eligible patients according to enrollment.

<table>
<thead>
<tr>
<th></th>
<th>Not enrolled (n = 154)</th>
<th>Enrolled (n = 281)</th>
<th>Total (n = 435)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.46 ± 13.91</td>
<td>57.23 ± 12.87</td>
<td>56.96 ± 13.24</td>
<td>0.564†</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>103.02 ± 12.93</td>
<td>103.85 ± 13.43</td>
<td>103.55 ± 13.25</td>
<td>0.535‡</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>127.52 ± 18.19</td>
<td>129.66 ± 16.12</td>
<td>128.85 ± 16.90</td>
<td>0.177†</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>82.05 ± 11.82</td>
<td>81.16 ± 10.59</td>
<td>81.47 ± 11.04</td>
<td>0.423‡</td>
</tr>
<tr>
<td>Number of medications</td>
<td>4.11 ± 2.19</td>
<td>3.71 ± 2.14</td>
<td>3.97 ± 2.18</td>
<td>0.070†</td>
</tr>
<tr>
<td>Type 2 Diabetes Mellitus (Y/N)</td>
<td>Yes = 52</td>
<td>Yes = 93</td>
<td>Yes = 145</td>
<td>0.888§</td>
</tr>
<tr>
<td>No = 102</td>
<td>No = 188</td>
<td>No = 290</td>
<td>No = 379</td>
<td></td>
</tr>
<tr>
<td>Records of CVD (Y/N)</td>
<td>No = 126</td>
<td>No = 233</td>
<td>No = 359</td>
<td>0.759§</td>
</tr>
<tr>
<td>Yes = 117</td>
<td>Yes = 66</td>
<td>Yes = 103</td>
<td>Yes = 332</td>
<td></td>
</tr>
<tr>
<td>Sedentary (Y/N)</td>
<td>No = 37</td>
<td>No = 215</td>
<td>No = 322</td>
<td>0.909§</td>
</tr>
<tr>
<td>Yes = 29</td>
<td>Yes = 44</td>
<td>Yes = 73</td>
<td>Yes = 104</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td>No = 88</td>
<td>No = 170</td>
<td>No = 258</td>
<td>0.676§</td>
</tr>
<tr>
<td>Former = 37</td>
<td>Former = 67</td>
<td>Former = 104</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure control</td>
<td>Adequate = 95</td>
<td>Adequate = 171</td>
<td>Adequate = 266</td>
<td>0.865§</td>
</tr>
<tr>
<td>(adequate/not adequate)</td>
<td>Not adequate = 59</td>
<td>Not adequate = 110</td>
<td>Not adequate = 169</td>
<td></td>
</tr>
</tbody>
</table>

kg = kilograms; m = meters; cm = centimeters; Y/N = yes/no; CVD = cardiovascular disease; ISH = isolated systolic hypertension; * According to the VI Brazilian Guidelines in Arterial Hypertension7; † Student’s t test; ‡ Chi-square; § Chi-square
A female-majority sample (62.91%) was identified, with mean age 57.75 ± 12.48 years old. One hundred and twenty-eight (60.09%) individuals were adherent to medication and 68 (31.92%) were diabetic. Only 43 diabetic individuals had HbA1c levels registered in the medical charts, with a median level of 7.38 (6.7 – 8.0).

Mean duration of cohort follow-up was 18.70 ± 4.67 months. There were no significant differences in BMI and weight from baseline till the end of the cohort. Median SBP at admission was 130 (120–140), and diastolic BP was 80 (70 – 85). At the end of follow-up, median SBP was 130 (120 – 136.66); measures for diastolic BP were 80 (76.66 – 86.66). Eighty-five patients (39.90%) did not meet BP goals.

When categorized to a binary variable, BP control was significantly associated to T2DM (χ²; p < 0.001), medication adherence (χ²; p = 0.009) and polypharmacy (p < 0.001). Among the previously mentioned characteristics, only T2DM was found significant by the univariate analysis of variance (R-squared = 0.677; F = 267.413; p < 0.001).

In the logistic regression model, the binary outcome of BP control was considered an independent variable, whereas the variables age, gender, polypharmacy, medication adherence, weight, BMI and T2DM were dependent factors. After the first round, non-significant variables from the model (weight, BMI, age and medication adherence) were removed to control potential confounders. From this final model, polypharmacy (5 drugs or more), with an OR 1.465 (p = 0.01), female gender (OR 3.110; p = 0.031) and the presence of T2DM (OR 0.003; p < 0.001) proved to be the predictors of uncontrolled BP in the cohort. (Supplementary material)

The addition of one drug increases 1.4 times the odds of the individual to sustain BP levels off the goals (CI 1.092 – 1.966). Diabetes was a protective factor, reducing by 99.7% the chances of having uncontrolled BP when compared to non-diabetic patients (CI 0.000 – 0.026). Females are 3.1 times more likely to have higher than expected BP when compared to males (CI 1.109 – 8.717).

Discussion

Correlations between aging, arterial stiffness and hypertension are well established (AlGhatrif & Lakatta, 2015; Faconti, Bruno, Ghiadoni, Taddei, & Virdis, 2015). Endothelial dysfunction also has important implications in blood pressure control (AlGhatrif et al., 2013; Sun, 2015).

Despite strong epidemiologic evidence associating higher prevalence of hypertension with aging (AlGhatrif et al., 2013; Beckett et al., 2012; Hatori et al., 2012; Sociedade Brasileira de Cardiologia et al., 2010; Sun, 2015), correlations between long term blood pressure control and age still seems unclear (Adedapo, Sikude, Adeleke, & Okechukwu, 2012; Beckett et al., 2012; Berlowitz et al., 1998). Confounding factors may hamper the analysis of age in hypertension control. Consequently, the presence of comorbidities and polypharmacy, common in this age group, may directly interfere with BP control.

Impact of age on this outcome was not detected, while other studies did (AlGhatrif et al., 2013; Sun, 2015). According to the Baltimore Longitudinal Study of Aging, age was found to be one of the main longitudinal determinants of hypertension control and its effects persist even in the prehypertensive range (AlGhatrif et al., 2013).

Medication adherence was previously found to be associated with BP control in cross sectional studies (Kang et al., 2015; Yue, Bin, Weilin, & Aifang, 2015). In one study (Kang et al., 2015), however, only younger patients’ adherence was correlated with BP control, whilst only high SBP was correlated with adherence in a study by (Yue et al., 2015). Medication adherence did not interfere with BP control in current sample.

Polypharmacy was previously pinpointed as interfering with BP control (Benetos et al., 2015; Raebel et al., 2012). In one multicenter retrospective study, the authors found an association with lower medication adherence and persistence of high BP, cardiovascular disease and increased health care costs (SicrasMainar et al., 2013). Our findings demonstrated that the higher the number of medications used, the greater were the chances of having uncontrolled BP at the end of the cohort. By observing trends in antihypertensive medication use and BP control among U.S. adults with hypertension, the authors discovered an important increase in the proportion of hypertensive patients taking multiple antihypertensive agents, especially people using polypharmacy regimens to meet BP goals (Gu, Burt, Dillon, & Yoon, 2012). Inappropriate therapy potential should not be neglected, especially in older hypertensive patients; a rational combination of medications should be considered to maximize BP control.

Several contributing factors may explain why blood pressure control differs in males and females (Shaw & Protheroe, 2012). Beside the theoretical relationships between BP control and muscle sympathetic nerve activity (Shaw & Protheroe, 2012), there is no information to date that suggests chromosomes alone may affect hypertension control.
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(Maranon & Reckelhoff, 2013). Nevertheless, it has been systematically shown that premenopausal women have lower BP than age-matched men (Maranon & Reckelhoff, 2013; Yanes & Reckelhoff, 2011). The role of androgens in BP control and hypertension is not clear (Maranon & Reckelhoff, 2013). Evidence suggests that estrogens may attenuate sympathetic activity (Holt et al., 2013; Joyner, Wallin, & Charkoudian, 2015; Maranon & Reckelhoff, 2013). Current sample showed a slight predominance of women, with average age close to the menopause period. These characteristics may explain current findings with regard to an increase of 3.1 in the odds ratio for poor blood pressure control in women.

Lower chances of poor BP control in hypertensive patients with diabetes were detected when compared to non-diabetic ones. In a German longitudinal study (DIAB-CORE Consortium) hypertension control was achieved only in about half the number of people with T2DM (Rückert et al., 2015). Possible explanations for current findings may include better engagement of T2DM patients with regard to the clinical control of comorbidities. Previous authors found that after diabetic and hypertension therapy group sessions, BP was better controlled, with a persistent effect after the educative strategy (López-Portillo, Bautista-Vidal, Rosales-Velásquez, Galicia-Herrera, & Riveray Escamilla, 2007).

Although current study has its limitations, it provides interesting contributions to the literature. Limitations inherent to the study design include the separation of the effects of the main exposition factors from those produced by extrinsic and confused variables, with the risk of masking possible associations between exposure factor and disease, over- or under estimating the results of the study. It may be acknowledged that cultural and socio-economic factors would change the prevalence of some exposure variables. Outcome was evaluated as a dichotomous or numerical response (average of three or more BP measurements in outpatient visits). Further, the white-coat effect may not be neglected and actually it has not been evaluated.

Anyway, cohort designs have advantages over traditional cross-sectional studies, since they allow a better association between exposure variables and the outcome studied. Current study provides a longitudinal analysis of the interference of traditional cardiovascular risk factors in controlling blood pressure in the short and medium terms, identifying interesting gaps for future research. Even though medication adherence was indirectly evaluated, more complex assessments of engagement level of patients with pharmacological and non-pharmacological treatment for high blood pressure will be timely, especially in diabetic patients.

Conclusion

No interference of age or medication adherence in blood pressure control was reported in the prospective cohort of hypertensive patients. In fact, the higher the number of medications in use, the greater was the chance of having blood pressure control out of goals.

Female gender was associated with a 3.1 increase in the odds ratio of poor blood pressure control. Compared with non-diabetic hypertensive patients, the hypertensive diabetic patients had lower chances of poor blood pressure control. A possible reason for this last finding includes higher levels of attention to the control of comorbidities by the multidisciplinary team.

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