Validation of the electronic prescription as a method of measurement of treatment adherence in hypertension

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Background. The diagnosis of non-adherence is complex and there are no completely reliable methods that can be used widely in daily practice. The aim of this study was to validate electronic prescriptions as a method of measuring treatment adherence in patients with mild-moderate hypertension.

Methods. We conducted a prospective, longitudinal, multicenter study in primary care centers. The study involved 120 patients treated for hypertension and included in the electronic prescription program of the centers. Five visits were made: initial, 6, 12, 18 and 24 months. Adherence was measured using an electronic monitor [medication event monitoring system (MEMS)] and through the electronic prescription program. We calculated the adherence rate (AR) using the MEMS and the electronic prescriptions, with the Medication Possession Ratio (MPR). Adherent patients were considered to be those whose AR was 80-100%. To validate the electronic prescription, its data were compared to the pill count by MEMS (Method of certainty). Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, and positive (LR+) and negative (LR-) likelihood ratios were calculated. The Kappa concordance index and the area under the ROC curve were also determined.

Results. The study was completed by 108 patients (mean age 61.06 years, SD 9.08). Adherence was 77.4% by MEMS (95% CI: 66.8-88%) and 80.4% (95% CI=70.3-90.5) by MPR. At 24 months the sensitivity was 87%, specificity 93.7%, PPV 80%, NPV 96.1%, LR+ 13.8 and LR- 0.1. The K was 0.782 and the AUC was 0.903 (95% CI: 0.817-0.989). Therapeutic complexity was associated with pharmacological non-adherence (OR=1.35, p<0.01).

Discussion. The electronic prescription was an excellent method to measure non-adherence in hypertensive patients included in this program for over two years. Therapeutic simplicity improved treatment adherence.

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Abstract

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Introduction

Control of hypertension, together with control of different vascular risk factors, is essential in preventing cardiovascular disease.[1-2] This importance relates to avoiding preventable cardiovascular events because they have a great impact on society, in terms of both morbidity and mortality.[3-4] Achieving the objectives of blood pressure (BP) control requires knowing the possible causes associated with lack of control. Among the main causes are therapeutic inertia [5-6] and non-adherence to treatment.[7] The magnitude of non-adherence is very important and many reasons exist for patients not taking their medication properly. Indeed, sometimes the patient is not even aware of being non-adherent[8] (forgetfulness, changes in dosage, waits to have symptoms, etc.). It is therefore essential to identify patient adherence in order to provide tools to enable improvement.

The diagnosis of non-adherence is complex and there are no completely reliable methods that can be used widely in daily practice.[9] Since the advent of electronic prescriptions and, subsequently the use of the XXI Prescription program in Andalusia,[10] this electronic prescribing system is being used by health professionals in chronic diseases as a tool or method to measure adherence, though without knowing if it is truly valid. XXI Prescription is a new model of prescription and medication supply which allows into a single act to prescribe all drugs required by the patient, for a maximum of one year. Due to the lack of indirect methods to obtain adequate indicators of validity and the importance of these measurement methods, they should be used in medical consultation to rule out therapeutic non-adherence before making treatment decisions. The aim of this study, therefore, was to validate the electronic prescription (XXI Prescription) as the measurement method for adherence to antihypertensive therapy in the treatment of mild-moderate hypertension in primoy care setting.

Materials & Methods

This is a prospective, longitudinal, multicenter health outcomes research study (Figure 1). It was carried out in primary care centers in urban health.

We included 120 outpatients of both genders, aged between 40 and 80 years, diagnosed with mild to moderate essential hypertension according to ESH-ESC 2007 and on antihypertensive therapy, with the diagnosis of hypertension registered in the medical record and incorporated in the electronic prescription program at least 3 months before the study and who gave their written consent. Patients with any of the following criteria were excluded: pregnant or breastfeeding women, patients who had diseases that could interfere with the development of the study, inability to give informed consent, participants in research studies or other patients who had a cohabitant taking the same antihypertensive medications.

Of the 120 patients, 102 completed one year of follow-up. We were unable to evaluate 18 patients. Using a 95% confidence interval (95% CI) and expecting to find an area under the ROC (AUC) curve of 0.9, with an expected AUC different from 0.5, our sample size achieved a statistical power of 99.5%.

The study began in January 2010 and concluded in December 2012. The enrollment period was 6 months and the mean follow-up was two years. Five visits were made to the health center: the enrollment visit, at 6, 12 and 18 months and the final visit at 24 months.

1. At the enrollment visit the inclusion and exclusion criteria were confirmed. In addition, informed consent was obtained, the medical history was taken and weight, height, waist circumference and BP were measured. BP was measured twice with sphygmomanometer on the same arm. On this visit each patient was given a medication event monitoring system (MEMS)

for each antihypertensive drug prescribed in the XXI electronic prescription. The use of the MEMS was explained in accordance with the health center protocol on their use. The patients were instructed to open the container cap daily, take the medication, and then close the cap. The name of the drug was written on a label attached to the outside of the MEMS bottle. The bottle had to be brought to all appointments for a computer reading and the patients were trained to insert the corresponding month's tablets at the time of the opening the MEMS to take a dose. They were given an appointment at the health center for 6 months later.

2. At the follow-up visits weight, height, waist circumference and BP were measured. The MEMS reading was downloaded and subsequently analyzed using a computer program. The number of openings was validated, eliminating any erroneous openings. The dispensing of the drug recorded in Diraya (the digital medical record used in the Autonomous Community of Andalusia) was noted from the dispensation module in the pharmacy. In the case of failure to achieve the therapeutic objectives,[1] this was reported to the attending physician, and if the physician prescribed another drug, it was replaced in the MEMS bottle by the patient. At the final visit the MEMS bottles were collected.

3. Treatment adherence was measured by the MEMS and the electronic prescription program. The pill count using the MEMS was used as a method of certainty to assess adherence.[11] To validate the electronic prescription its data were compared with the pill count using MEMS on a 2×2 table to calculate the indicators of validity.

The following variables were analyzed: age and gender, number of chronic diseases and the number of drugs taken, cardiovascular risk factors, body mass index (BMI) and abdominal waist circumference; the mean clinical BP (SBP and DBP) with their SD and the differences between

two consecutive visits and between the start and end of the study. We calculated the adherence rate (AR) using MEMS and the electronic prescription (MPR) according to the formula: AR per MEMS: Total number of tablets presumably taken-MEMS openings / total number of tablets that should have been taken according to dosage (days elapsed) x 100. MPR per electronic prescription: Total number of tablets presumably taken-purchased from the pharmacy / total number of tablets that should have been taken according to dosage (days elapsed) x 100. The AR between two consecutive visits was calculated from the MEMS, as well as the cumulative AR at each visit from the start. The AR at study completion was considered to be the cumulative AR at study completion or at withdrawal from the study for any reason, provided that a pill count was performed. The MPR was considered in a similar way. The degree of hypertension control was assessed and considered controlled when the BP was less than 140 and 90 mmHg for SBP and DBP, respectively. The main variable was the percentage by MEMS of the patients who adhered to all the doses. This variable was used to classify the patients as adherent, AR≥80%, or non-adherent, AR<80%. The MEMS was also used to determine the percentage of days the user took one tablet daily, the percentage of doses taken in the recommended time frame (7-9 hours) and the therapeutic coverage or time during which the patient was pharmacologically covered by an antihypertensive drug, assuming the drug was effective for 24 hours. Data were collected in a Microsoft Excel database and the SPSS PC+s15 computer analysis program was used. All the variables were calculated and compared according to two criteria: 1. Globally, 2. Between adherent and non-adherent patients.

To validate the electronic prescription, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were calculated. The Kappa concordance index and the ROC curve or diagnostic

performance curves to detect the discriminatory power of the test were also determined. This is used to confirm two diagnostic tests by calculating the area under the curve, and the closer the value is to 1, the greater the discriminatory power of the test. A descriptive statistical analysis was performed and in the bivariate analysis the Chi square test and the Student's *t*-test were used to compare qualitative and quantitative variables, respectively. In addition, a backward stepwise multivariate logistic regression analysis was performed comparing the variables between adherent and non-adherent patients. $p<0.05$ was considered significant and confidence intervals were calculated at 95%. The Paradox 3.5 database and SPSS PC+s15 software were used for this study. The study was conducted following the ethical standards for clinical research of the Declaration of Helsinki. The study was approved by the Research Committee of the Health Area of Huelva.

Results

Of the 120 patients initially included, data were obtained from 102 (85%). The causes for exclusion of patients from the study were technical problems with the MEMS in 4 cases, loss of the MEMS in 3 cases, the MEMS not being used conscientiously by the patient in 6 cases, 2 patients requested to leave the study, one moved to another city, one developed a tumor, and one with white-coat hypertension who did not require subsequent antihypertensive treatment. Thus, 18 patients were excluded because the four pill count measurements were not obtained with the MEMS. All 102 patients included completed the four follow-up visits over the two years.

The overall mean age was 61.06 years (SD 9.08), with an age range of 40-80 years; there were 32 men (31.4%) and 70 women (68.6%) (p=not significant for age or gender). The mean initial SBP and DBP were 139.2 (SD 15.9) and 81.1 (SD 9.1), respectively, and the final means were 139.1 (SD 15.3) and 83 (SD 10.1). The percentage of hypertensive patients who were controlled

at the initial visit, and at 6, 12, 18 and 24 months, was 51% (CI=41.4-60.5%), 62.7% (CI=53-71.7%), 66.7% (CI=57-75%), 66.7% (CI=57-75%) and 42.2% (CI=33-51.8%), respectively. The percentage of controlled patients decreased at the final visit (p=0.01).

The mean percentage of doses taken was 89.1% (95% CI=81-97%), the mean percentage of days on which the dose of antihypertensive medication was taken properly was 83% (95% CI=73.6-92.6%) and the percentage of days on which the medication was taken at the correct time (8:00-9:00 a.m.) was 79.4% (95% CI=69.1-89.7%). The therapeutic coverage, assuming an antihypertensive effect of 24 hours, was 89.1% (95% CI=81.2- 97%). The AR according to the electronic prescriptions measured by MPR was 91.9% (95% CI=85-98.8%). Table 1 shows the mean AR calculated by MEMS and by MPR per visit.

Of the 102 participants, 77.4% (95% CI: 66.8-88%) were adherent overall, 70.6% (95% CI: 59-82.2%) adherent once daily, and 60.8% (95% CI: 48.4-73.2%) adherent at the correct time. According to the MPR, 80.4% of the patients (95% CI: 70.3-90.5%) were adherent. Table 2 shows the data per visit.

The sample was distributed into adherent and non-adherent subjects, with 79 being adherent and 23 non-adherent, and the possible influence of different variables on adherence was analyzed. When comparing both groups (Table 3) in both the bivariate and multivariate analysis, differences were only observed in the number of drugs taken (OR=1.35, $p<0.01$).

Blood pressure values per visit for adherent and non-adherent participants are shown in Table 4. Throughout the study there was a non-significant decrease in SBP. In the adherent group, at the initial visit the SBP was 138.8 (SD 16.8) and DBP 80.6 (SD 9.6) compared to 136.5 (SD 13.6) and 80.9 (SD 9.1) at the final visit, respectively. In the non-adherent group there was a

significant increase in SBP between the initial visit, 139.1 (SD 13.4) and DBP 81.6 (SD 7.6), and the final visit, 150.6 (17.3) and 92.2 (SD 9.2), respectively, ($p=0.04$ for SBP and $p=0.007$ for DBP). There were no differences between the groups during the course of the visits, except at the final visit, where the non-adherent group had a higher BP ($p<0.0001$). Assessing the degree of hypertension control between adherent and non-adherent patients showed that control at the initial visit was higher in the adherent group, though the difference was not significant. However, significant differences between the two groups were noted at visits 1, 2 and the final visit, with control being lower in the non-adherent group. Thus, at visit 1, 68.3% had controlled BP in the adherent group compared to 43.4% in the non-adherent group; at visit 2, 70.8% of the adherent group had controlled BP versus 52.2% in the non-adherent group. On completion of the study, control of hypertension in the adherent group was 50.6% (95% CI: 37.9-63.3) versus 13% (95%: 4.4-21.6) ($p<001$) in the non-adherent group.

At the final visit at 24 months, the sensitivity was 87% (95% CI: 65.3-96.6%), specificity 93.7% (95% CI: 85.2-97.7%), PPV 80% (95% CI: 58.7-92.4%), NPV 96.1% (95% CI: 88.3-99%), LR+ 13.8 and LR- 0.1. Agreement using the Kappa index improved from the initial 0.292 to reach good agreement at the last visit of 0.782 (Table 5). The following values were obtained for the areas under the curve for the electronic prescription: 0.618 (95% CI: 0.471-0.766) at the first visit, 0.695 (95% CI: 0.596-0.844) at the second visit, 0.813 (95% CI: 0.705-0.922) at the third visit, and 0.903 (95% CI: 0.817-0.989) at the final visit (Table 6). Figure 2 shows the ROC curve with its area under the curve.

Discussion

The main objective of this study was to validate the XXI electronic prescription as a method of measuring adherence in hypertension.

Comparing the extent of non-adherence with previous studies on hypertension in Spain using pill count or MEMS shows that adherence has improved in recent years. The mean AR ranged between 74.04% in the Puras 2001[12] study and 92.5% in the Cumampa 2005[13] study. In the Comple study[14], which used MEMS in hypertensive patients at high vascular risk with 6 months of follow up, the mean percentage of overall doses taken was 87.9%, the mean percentage of days on which a daily tablet was taken was 73.4%, the percentage of days the medication was taken at the prescribed time was 63.17%, and therapeutic coverage for 24 hours was 82.4%. These data are similar to the results of our work with 24 months of follow up.

Calculating the AR by MEMS and electronic prescription per visit gave a higher percentage of mean adherence throughout the study for all parameters except the mean MPR percentage, with no significant difference throughout the visits and the percentage of overall adherence at the third and fourth visit being the same.

The percentage of adherent patients with an AR higher than 80% was similar to that found in other series, such as the Cumple II study,[14] with an overall 73.3% of adherent patients. The percentages compared to the once-daily adherent patients and those who took their medication at the correct time decreased. The same occured in the Cumple II study, where these percentages of correct dose and schedule were 52.8% and 46.5%, respectively. This reflects the difficulty of taking medication in general, which is compounded if it must be taken every day and in accordance with the schedule recommended by the physician. Regarding the percentage of adherent patients by MPR, we saw a significant decline in adherent patients throughout the visits, but this approached the percentage obtained with the MEMS. Bivariate and multivariate analyses were performed between the different study variables to assess their impact on adherence.

Significant differences were only observed for the number of drugs taken. Therefore, therapeutic complexity affects adherence, as has been shown in other studies.[15-16]

What was most striking about the relationship to BP control (Table 4) was the significant increase in both the mean systolic and diastolic BP in the non-adherent group at the final visit. This resulted in very significant differences at this visit between adherent and non-adherent subjects. This increase in BP was not seen at previous visits, although it should be noted that these were mean BP. It should be mentioned that at the 6-month visit, a significant decrease in SBP was seen in the adherent group, which was sustained at the 1-year visit. We must emphasize that the control of hypertension from the first visit was higher in the adherent group; though the differences were not significant, they were nevertheless evident at the first, second and final visits, with poorer control in the non-adherent group. This indicates that only a small percentage was well controlled in the non-adherent group, while 50% of the adherent group was controlled, with half of these patients taking the correct drug treatment at the two-year follow up. This compares with previous studies such as the PREVENCAT,[17] with 32.8%; Prescap,[18] with 41%; and Hicap studies,[19] with 39.3% of hypertensive patients controlled. Finally, we note that when associated with other cardiovascular risk factors, BP control decreased, with control being lower with an increased cardiovascular risk.[19]

To answer the question of whether the electronic prescription is valid, the pill count using MEMS was considered the gold standard in this study. Comparing the overall measurements of the adherent group by MEMS and by MPR (electronic prescriptions) showed the only significant differences to be at the first visit (Table 2). At all the other visits the percentages of adherent subjects remained similar, with no differences at the third and fourth visits. This can be interpreted as the MPR at the first visits being overvalued, since at the start of treatment the

patients tended to collect the medication from the pharmacy whether they took it or not. But when a patient had had the drug prescribed for some length of time and accepted this, only the treatment they were going to take was collected and tablets were not accumulated at home.

At the first visit the Kappa index indicated a weak agreement, but at the 18- and 24-month visits there was strong agreement between the two methods. The validity of the test showed that the sensitivity, or the ability to detect non-adherent subjects, was low at the beginning of the study, owing to the increase in false adherent subjects (false negatives), who accumulated drugs and were not detected by the method. However, with the successive visits the sensitivity improved and was high at the final visit because the electronic prescription (MPR) had detected the true non-adherent subjects (true positives).

The specificity or ability of the test to detect the adherent patients was high from the beginning. This is primarily because there were few false non-adherent patients (false positives) in the sample compared to the true adherent patients. One might assume, therefore, that it is difficult to take the medication if it is not collected from the pharmacy.

The PPV of the test improved at the successive visits. However, the NPV was high from the beginning and remained so at the successive visits. Therefore, it was at the final visit after two years where powerful values were observed for all the study tests. Analysis of the AR showed that both the LR+ and the LR- improved during the follow-up, such that at the final visit, confirmation of non-adherence (above 10) or ruling it out (equal to 0.1) was conclusive.[20]

When compared with other indirect methods to measure adherence, the best indicators of validation were obtained using electronic prescriptions. In the Haynes-Sackett test, or self-reported adherence test, the estimated sensitivity (35%), specificity (95%), predictive values and

likelihood ratios, comparing this with the counts of tablets still to be taken, were taken as proof of certainty in patients being treated with antihypertensive drugs.[20]

In assessing the areas under the ROC curve, the values for the XXI Prescription at the different visits improved from an average diagnostic test (AUC=0.618) to a very good diagnostic test at the fourth visit (AUC=0.903). We can conclude, therefore, that this test to measure adherence using the XXI Prescription in patients included in an electronic prescription program for more than two years in primary care has very good discriminatory diagnostic capacity.

Therefore, we propose to the SEH-LELHA[21] a practical modification to detect non-adherence (Figure 3); the Haynes-Sackett self-reported adherence test. If the patient claims to be non-adherent, they shall be deemed as such. If the patient maintains they have good adherence and their BP levels are within controlled values, they will be classified as adherent, since our goal is to control hypertension. If the patient claims to be adherent but the BP is not controlled, non-adherence should be suspected, and subsequently a query of their electronic health history in the medication module should be carried out to verify whether the drug has been included in an electronic prescription program for more than two years. If so, the dispensing will be checked and the MPR of the last six months will be performed. If there is no medication prescribed by electronic prescription or if the prescription is for less than 2 years, a pill count will be conducted, either at home, at the office visit or by telephone interview.

This study can be considered representative of the general population of uncontrolled hypertensive patients included in the electronic prescriptions program and treated in primary care, as an adequate sample calculation was justified. The sample was obtained by consecutive sampling with patients from different researchers in different basic health areas, with 100% of

those with pill counts completing the 5 visits over the 2 years of follow-up. This study met the criteria recommended by Haynes et al[22] for adherence studies. Thus, the diagnosis of hypertension was correct; the method of measuring adherence, the MEMS, has been validated; and the results on adherence and hypertension were assessed with a follow-up of 80% of the sample in over 100 individuals. At the same time, awareness of the study, use of the MEMS and control by two medical researchers may have conditioned a greater intensity of the intervention by the physician. However, these limitations are assumed in observational studies of health effectiveness in clinical practice and clinical effectiveness.[23]

To minimize information bias, the use of the MEMS was explained to all the patients at the initial visit. This first visit was carried out by the primary care physician from the health center with the collection of data in CRD, while the subsequent visits were conducted by two research doctors, thus avoiding measurement bias. To minimize reporting bias, the selected patients were included as having hypertension in the Diraya Health History program at the Health Center and on follow-up with chronic prescriptions. In addition, another possible bias was that which can occur when treating hypertension in primary care in patients assigned to an electronic prescription program and not generalizable to the general population.

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Table 1(on next page)

Mean percentage counts of adherence according to different variables calculated by the electronic monitors (MEMS) and by electronic prescription with the medication possession ratio (MPR) per visit

Table 1: Mean percentage counts of adherence according to different variables calculated by the electronic monitors (MEMS) and by electronic prescription with the medication possession ratio (MPR) per visit

	VISIT 1	VISIT 2	VISIT 3	VISIT 4	p
Total doses taken, %±SD	86.5±24	89±22.3	90.5±15.3	90.2±17.5	<0.01
Days on which 1 tablet was taken daily, %±SD	79±24.9	83.2±21.3	85.7±14.5	84.8±16.1	<0.01
Days the medication was taken during the prescribed time (7-9 hours),%±SD	76±30	80.2±25.1	77.2±25.1	84.0±17.7	<0.01
24- hour therapeutic coverage, %±SD	86.6±22.1	88.8±19.9	90.2±13.1	90.8±14	<0.05
MPR, %±SD	92.6±11.5	92.3±13.8	90.7±14.1	92.1±11.7	NS

MPR

NS

Table 2(on next page)

Percentage of adherent patients per visit, according to different variables calculated by the electronic monitors (MEMS) and by the electronic prescription with the medication possession ratio (MPR) per visit

Table 2: Percentage of adherent patients per visit, according to different variables calculated by the electronic monitors (MEMS) and by the electronic prescription with the medication possession ratio (MPR) per visit

	V1	V2	V3	V4	p
Adherent patients who took all their doses, % (N)	78.4(80)	80.4(82)	74.5(76)	77.5(79)	NS
Days on which adherent patients took 1 tablet daily, % (N)	66.7 (68)	70.6(72)	72.5(74)	74.5(76)	NS
Adherent patients who took medication during the correct time, % (N)	62.7(64)	60.8 (62)	58.8(60)	60.8(62)	NS
Adherent patients by MPR, % (N)	89.2(91)	83.3(85)	73.5(75)	75.5(77)	<0.05

NS: non-significant

Table 3(on next page)

Analysis of variables that could influence treatment adherence

Table 3: Analysis of variables that could influence treatment adherence

	ADHERENT PATIENTS N = 79	NON-ADHERENT PATIENTS N = 23	P
Age (years)	60.7 (SD 9.5)	59.7 (SD 7)	NS
Gender	M:27 (34.2%) F: 52 (65.8%)	M: 5 (21.7%) F: 18 (78.3%)	NS
Number of diseases	2.4 (SD 1.1)	3 (SD 1.4)	NS
Number of drugs taken initially	1.9 (SD 1.2)	3.9 (SD 1.9)	0.02*
Initial BMI	30.7 (SD 5)	32 (SD 5.5)	NS
Initial abdominal waist circumference	101 (SD 10.2)	101.2 (SD 10.2)	NS
Initial SBP	138.8±16.8	139.1±13.4	NS
Initial DBP	80.6±9.6	81.6±7.6	NS
Years with hypertension	6.6 (SD 3.8)	6.9 (SD 4)	NS
Antihypertensive drugs added during the study	15 (19 %)	5 (21.7 %)	NS
Age as CVRF	37 (45.7%)	11 (52.4%)	NS
Family history of CVD	10 (12.6%)	2 (8.7%)	NS
Diabetes	22 (27.8%)	3 (13%)	NS
Dyslipidemia	39 (49.4%)	11 (47.8%)	NS
Smoker	6 (7.6%)	2 (8.7%)	NS
Obesity	41 (51.2 %)	12 (52.2%)	NS
LVH	9 (11.4%)	3 (13%)	NS
Microalbuminuria	3 (3.8 %)	2 (8.7%)	NS
Retinopathy	2 (2.5%)	2 (8.7%)	NS
Coronary heart disease	4 (5 %)	3 (13 %)	NS
PVD	1 (1.2 %)	2 (8.7%)	NS
Stroke	3 (3.8 %)	2 (8.7%)	NS

Results expressed as mean and standard deviation (SD) or number of patients and percentages.

* Multivariate analysis OR=1.35 ($p<0.01$).

OR: Odds Ratio. NS: Not significant. BMI: Body Mass Index. SBP: systolic blood pressure. DBP: diastolic blood pressure. CVD: cardiovascular disease. LVH: left ventricular hypertrophy. PVD: peripheral vascular disease. CVRF: cardiovascular risk factor.

Table 4(on next page)

Mean systolic and diastolic blood pressure (SBP and DBP) by adherence group and per visit

Table 4: Mean systolic and diastolic blood pressure (SBP and DBP) by adherence group and per visit

	Initial visit	Visit 1	Visit 2	Visit 3	Final visit	p (Initial visit – Final visit)
Adherent						
SBP	138.8±16.8	133.8±17.6*	133.9±14.6*	135.7±14.5	136.5±13.6	NS
DBP	80.6±9.6	79.2±9.6	78.8±8.1	79±7.4	80.9±9.1	NS
Non-adherent						
SBP	139.1±13.4	137±14.5	133±15.5	133.9±14.8	150.6±17.3	0.04
DBP	81.6±7.6	82.3±8.3	79.2±8.9	80.7±8	92.2±9.2	0.007
p for differences in SBP by adherence groups	NS	NS	NS	NS	0.0001	
p for differences in DBP by adherence groups	NS	NS	NS	NS	0.0001	

* = $p<0.05$ compared to the value at the initial visit

Note: In this table, adherent patient has been defined as the patient being adherent at the final visit

Table 5(on next page)

Validation indicators

Table 5: Validation indicators.

	Visit 1	Visit 2	Visit 3	Final visit
Sensitivity	28.6%	50%	73.1%	87%
Specificity	95.1%	91.5%	89.5%	93.7%
PPV	60%	58.8%	70.4%	80%
NPV	83.7%	88.2%	90.7%	96.1%
LR+	5.8	5.9	6.9	13.8
LR-	0.8	0.6	0.3	0.1
Kappa index	0.292	0.413	0.618	0.782

PPV (positive predictive value). NPV (negative predictive value). LR+ (positive likelihood ratio). LR- (negative likelihood ratio).

Table 6(on next page)

Area under curve (AUC): Probability of detecting non-adherence by the methods studied.

Table 6. AUC: Probability of detecting non-adherence by the methods studied.

Diagnostic tests	AUC	SE[a]	Asymptotic significance[b]	Confidence interval 95 %	
				Lower	Upper
Electronic prescription visit 1	0.618	0.075	0.095	0.471	0.766
Electronic prescription visit 2	0.695	0.076	0.008	0.546	0.844
Electronic prescription visit 3	0.813	0.055	0.000	0.705	0.922
Electronic prescription Final visit	0.903	0.044	0.000	0.817	0.989

a: Nonparametric assumption

b: Null hypothesis: true area = 0.5

Figure 1(on next page)

Study chart: prospective, longitudinal, multicenter health outcomes research study

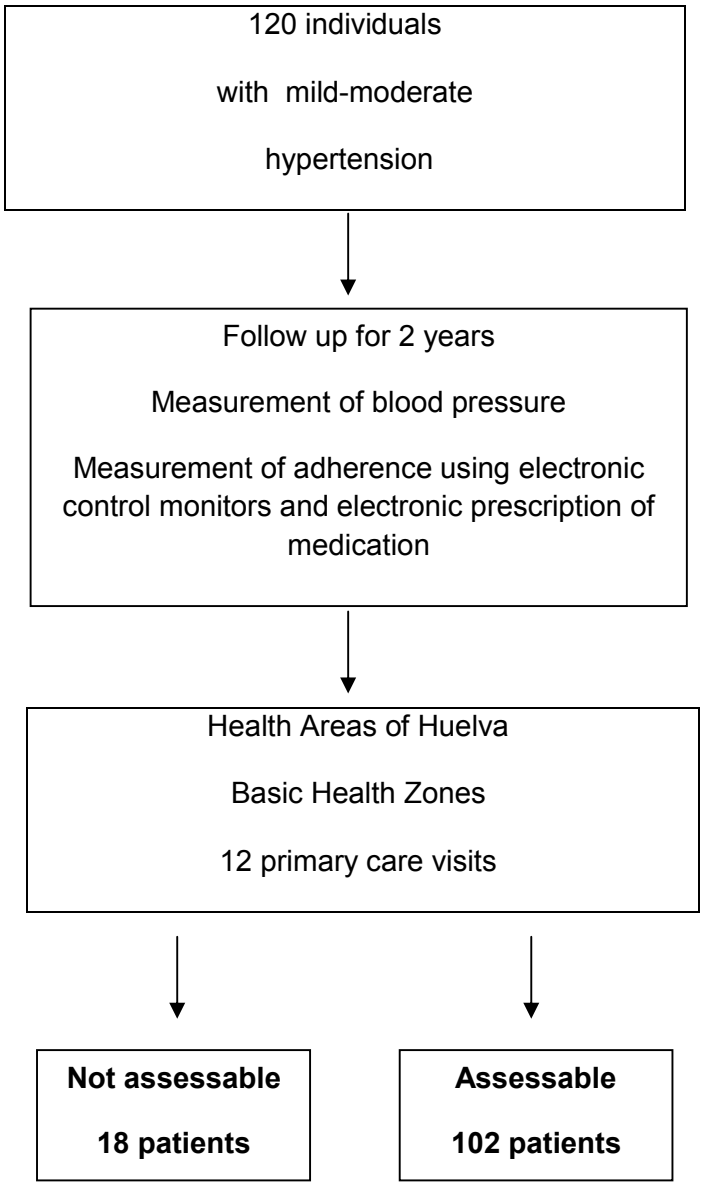
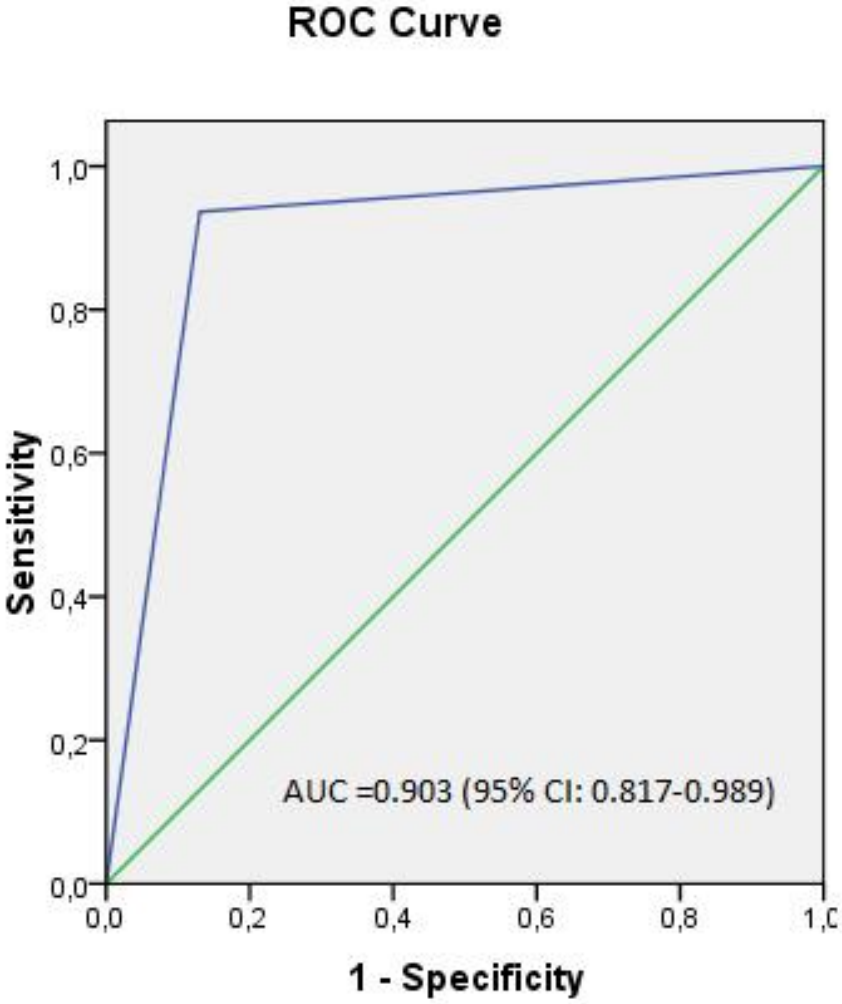


Figure 2(on next page)

ROC curves: probability of detecting nonadherence at visit 4 using the methods studied.



Diagonal segments are produced by ties.

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Figure 3(on next page)

Algorithm for measurement of adherence in hypertension recommended after the results obtained

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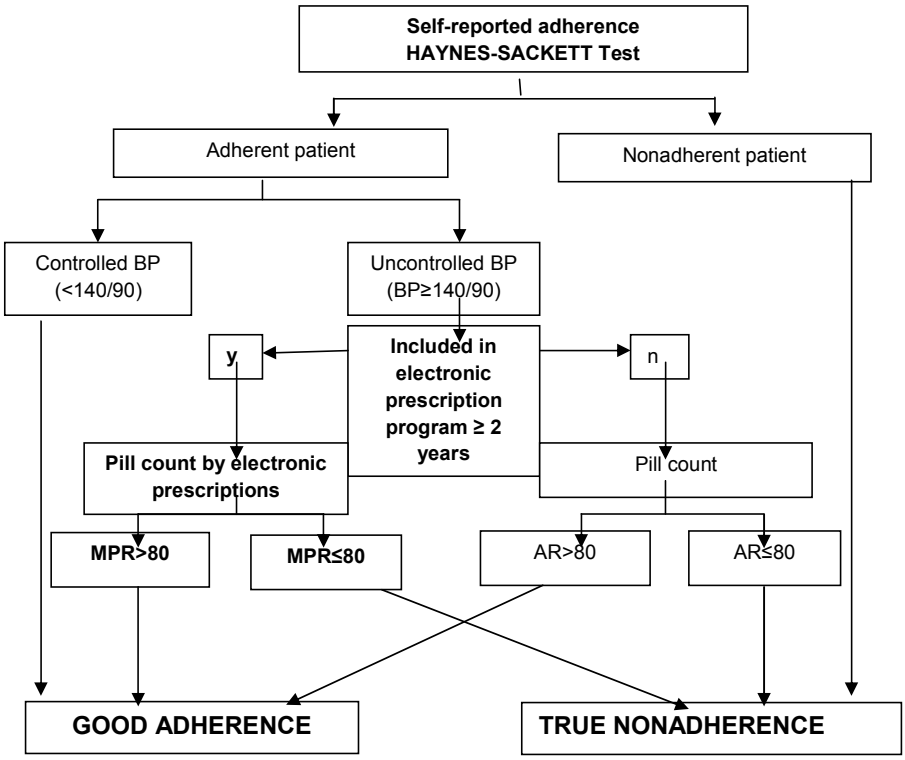

AR= Adherence ratio.

MPR= Medication Possession Ratio.

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