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## A MULTI-CENTER CLUSTER-RANDOMIZED TRIAL OF A MULTI-FACTORIAL INTERVENTION TO IMPROVE ANTIHYPERTENSIVE MEDICATION ADHERENCE AND BLOOD PRESSURE CONTROL AMONG PATIENTS AT HIGH CARDIOVASCULAR RISK (The COM99 study)\*

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### Abstract

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Conflict of Interest Disclosures: None.

**Background**—Medication non-adherence is common and results in preventable disease complications. This study assesses the effectiveness of a multifactorial intervention to improve both medication adherence and blood pressure control and to reduce cardiovascular events.

**Methods and Results**—In this multi-center, cluster-randomized trial, physicians from hospital-based hypertension clinics and primary care centers across Spain were randomized to receive and provide the intervention to their high-risk patients. Eligible patients were  $\geq 50$  years of age, had uncontrolled hypertension, and had an estimated 10-year cardiovascular risk greater than 30%. Physicians randomized to the intervention group counted patients' pills, designated a family member to support adherence behavior, and provided educational information to patients. The primary outcome was blood pressure control at 6 months. Secondary outcomes included both medication adherence and a composite end-point of all cause mortality and cardiovascular-related hospitalizations. Seventy-nine physicians and 877 patients participated in the trial. The mean duration of follow-up was 39 months. Intervention patients were less likely to have an uncontrolled systolic blood pressure (odds ratio 0.62; 95% confidence interval [CI] 0.50–0.78) and were more likely to be adherent (OR 1.91; 95% CI 1.19–3.05) when compared with control group patients at 6 months. After five years 16% of the patients in the intervention group and 19% in the control group met the composite end-point (hazard ratio 0.97; 95% CI 0.67–1.39).

**Conclusions**—A multifactorial intervention to improve adherence to antihypertensive medication was effective in improving both adherence and blood pressure control, but it did not appear to improve long-term cardiovascular events.

## Keywords

hypertension; medication adherence; blood pressure; intervention studies

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Hypertension is a major but modifiable contributory factor to cardiovascular diseases (CVD) such as stroke and coronary heart disease.<sup>1;2</sup> According to the Seventh Report of the Joint National Committee on Prevention, Detection and Treatment of High Blood Pressure in the United States (JNC-7), the percentage of patients whose blood pressure (BP) is under control (i.e.,  $< 140/90$  mmHg) increased from 10% in 1976–80 to 34% in the period 1999–2000. Nevertheless, BP control rates are far below the Healthy People 2000 goal of 50%.<sup>3–5</sup> The situation in Spain is similar with at best 40% of patients with hypertension under control.<sup>3;6</sup>

A major modifiable reason for the lack of BP control is medication nonadherence, where adherence is defined as the extent to which a person's behavior corresponds with the recommendations of their health care provider.<sup>7</sup> In general, poor adherence to medications is associated with the development of complications, disease progression, avoidable hospitalizations, premature disability and death.<sup>7–10</sup> The same is true for adherence to antihypertensive medications.<sup>11;12</sup>

Most previous adherence intervention studies share the following methodological limitations: a lack of patient-centered outcomes; limited statistical power; short duration of follow-up; unreliable measures of adherence; and limited generalizability due to their intensity and complexity.<sup>13;14</sup> The objective of this study was to assess the effectiveness of a simple, multi-factorial intervention aimed at increasing antihypertensive medication adherence, improving BP control, and reducing cardiovascular events in high-risk patients with uncontrolled hypertension. The intervention was designed to be implemented in resource-poor settings and combined behavioral, cognitive, and social support components. The behavioral component included counting pills in front of the patients. Counting pills by doctors is a routine activity in most clinical trials and patients tend to adhere better in clinical trials than in routine clinical practice.<sup>15;16</sup> Based on prior research, we hypothesized

that this Hawthorne effect could be used to improve medication adherence in routine practice.<sup>15;17</sup> In this study, adherence was monitored electronically, and study participants were followed for up to five years. A cluster-randomized design randomizing physicians was chosen to avoid within-physician contamination.

## METHODS

### Study design

The study was approved by the Ethics Committees of the Hospital General de Vic (Barcelona, Spain) and Hospital de la Princesa (Madrid, Spain). In this multicenter, cluster-randomized trial, participating physicians from hospital-based hypertension clinics and primary care centers across Spain were randomized in blocks of two within their site of practice. Block randomization was used to insure that physicians were balanced across intervention and control groups within hospitals and primary care clinics. Randomization was centralized through a single coordinating center and the sequence was concealed until interventions were assigned. A computer generated random number list was used to randomize physicians, and investigators were not aware of the randomization scheme. The trial was actively monitored by both internal and external quality control auditors.

### Participants

Patients were  $\geq 50$  years of age; they had uncontrolled essential hypertension, as defined by an average systolic blood pressure  $\geq 140$  mmHg and/or an average diastolic blood pressure  $\geq 90$  mmHg; and they had a calculated 10-year cardiovascular risk  $>30\%$  as defined by the WHO/ISH 1999 guidelines.<sup>18</sup> There were only two exclusion criteria – participation in another clinical trial in the preceding 3 months and refusal/incapacity to provide informed consent. There were two coordinating centers (in Catalonia and Madrid, Spain), which separately recruited physicians. Patients were recruited by their physicians after assessing eligibility. The coordinating center in Catalonia was also in charge of randomization, the validation of patients eligibility criteria, the provision and analysis of the Medical Events Monitoring Systems (MEMS) containers (Aardex Ltd., Zug, Switzerland), the provision and calibration of semiautomatic sphygmomanometers, data entry, and study quality control. Patients were recruited between January 2000 and July 2002, and were followed until December 2005.

We administered a survey to all study physicians to assess their characteristics across intervention and control groups. Sixty-nine (87%) out of 79 physicians who actively recruited patients answered the survey. Characteristics of recruiting physicians are depicted in Table 1. There were no differences in the survey response rate between control and intervention groups.

### Study Intervention

Patients in the control group received standard care but they followed the same schedule of visits as the intervention group. Patient in both groups had two baseline visits a week apart and prior to study initiation so as to insure that patient met study criteria. These baseline visits were followed by a study initiation visit in the same month during which patients in both groups received their MEMS devices; this visit constituted the start of the study. Follow-up visits occurred at 1, 3, and 6 months following study initiation, and thereafter every 6 months. Medication changes were not allowed in both groups until the 3-month follow-up visit unless there was intervening severe hypertension. The intervention to improve adherence in the treatment group lasted 6 months and consisted of three main components: 1) counting pills during physician visits; 2) designating a family member to support adherence behavior, and 3) providing an information sheet to patients at the start of

the intervention. Patients were supposed to bring back the information sheet at each follow-up visit. If they did not, they were provided a new sheet at the start of the follow-up visit.

The information sheet included information on each BP medication dose and frequency, potential medication side effects, what to do if a dose was missed, what to do when the medication was running low, and how different types of antihypertensive medication could be taken together. It also included two questions for the patient to complete prior to each visit – one question on any problems taking the medication since the last visit and the other question on whether the patient experienced any side effects. Space was provided on the information sheet for patients to record BP readings, including self-measurements, and their current antihypertensive regimen. Patients were encouraged to measure their BP every other week,<sup>19</sup> and they were given calendars to mark the day that they took their medication. All intervention physicians underwent an initial 2-hour session on motivational interviewing techniques to promote patient adherence.<sup>20</sup> Physicians were advised to avoid confrontation and to respect patients' autonomy. Case vignettes representing confrontational and motivational interviewing scenarios were used during the training.

### Outcome measures

The primary outcome was systolic and diastolic BP control at the end of the first 6 months of follow-up. Medication adherence over 6 months of follow-up was the secondary outcome. As an additional, exploratory outcome we included a composite end point of all cause mortality and admission to a hospital for any cardiovascular event at 5 years of follow-up. The end points were defined identically to those in the VALUE trial.<sup>21</sup> The end-points were adjudicated by a clinical events committee which was blinded to the patients' treatment group.

Three BP readings were obtained at each visit with a semiautomatic oscillometric BP monitor (OMRON 705-CP), which could print the readings. Each reading was printed and attached to the data collection instruments. The average of the three readings was used in the analysis.

Adherence was measured electronically using MEMS bottles (AARDEX Ltd., Zug, Switzerland) during the first 6 months of follow-up. Patients were informed of the MEMS functionality. Because of cost limitations, only one MEMS bottle was provided per patient, and fixed dose combination antihypertensive medications were encouraged when a patient required more than one BP medication. Therefore, when a patient was taking a fixed dose combination antihypertensive medication, that was the one introduced in the MEMS bottle. If the patient was not using combination medications, the drug the patient had been taking for the longest period of time was the one monitored electronically. The average number of antihypertensive drugs used was 2.2 (1.0, standard deviation [SD]) and the average number of drugs monitored electronically was 1.3 (0.4, SD). Accordingly, the average percentage of antihypertensive drugs monitored electronically per patient was 67% of those taken. For the medications monitored, we defined adherence as the percentage of days in which the correct number of doses was taken. Two additional adherence measures were assessed – medication-taking adherence and medication-timing adherence. Medication-taking adherence was defined as the percentage of prescribed doses taken, whereas medication-timing adherence was the percentage of prescribed doses taken on time. We allowed a 12 hour window for medication taken once daily and a 6 hour window for medications taken twice daily.

## Statistical Analysis

Sample size estimates accounted for the cluster-randomized design. Due to low initial enrollment, sample size estimates had to be downwardly adjusted from a cluster size of 25 patients per physician to 11 patients per physician. Assuming an intraclass correlation coefficient (ICC) of 0.05 and 12% of patients lost to follow-up, an enrolled sample size of 900 patients (i.e., 450 per arm) equated to an effective sample size of 264 patients per arm. Therefore, with 264 patients per arm and a type I error of 0.05, we estimated 80% power to detect a 3.9 mmHg change in SBP and a 2.7 mmHg change in DBP.

Continuous baseline variables were compared using either a two sample t-test or the Wilcoxon test. Categorical variables were compared using a chi-square test.

Outcomes were analyzed as intention-to-treat. Mean BP was analyzed using generalized estimating equation (GEE) repeated measures ANOVA. The GEE clusters were defined by multiple patients sharing the same physician and the up to three repeated measures (i.e., for the 1, 3, and 6-month visits) for each patient. As the distribution of adherence measures appeared to be exponential, GEE gamma and logistic regression models were used to analyze the continuous and binary measures of medication adherence, respectively. Non-adherence was defined as measured adherence of less than 80%. This cutoff is widely used and has been shown to be associated with hypertensive clinical outcomes.<sup>22</sup> The composite cardiovascular outcome was analyzed as time-to-event using Kaplan-Meier estimation and Cox proportional hazards regression models. Physician clusters were accounted for using the COVSANDWICH (AGGREGATE) option in Proc PHREG in SAS v9.1 (SAS Institute Inc, Cary, NC).<sup>23</sup> Statistical analyses were performed by an independent group blinded to group assignment. A two-sided alpha level of 0.05 was considered statistically significant.

## RESULTS

Between January 2000 and July 2002, 147 physicians were recruited and randomized to the control and intervention groups (Figure 1). Fifty-four physicians (24 in the control arm and 30 in the intervention arm) withdrew before recruiting any patients. Fourteen physicians (11 in the control arm and 3 in the intervention arm) withdrew study consent prior to their 40 patients starting follow-up. Twelve patients (5 in the control arm and 7 in the intervention arm) were excluded because of protocol violations. Eight patients (3 in the control arm and 5 in the intervention arm) did not have follow-up data. Therefore, 79 physicians (39 in the control arm and 40 in the intervention arm) and 875 of their patients (457 in the control arm and 418 in the intervention arm) were available for complete analysis. Among those, MEMS data were not available for 78 patients (8.9%) for different reasons (14 devices were lost, 2 patients never used the MEMS, 4 MEMS were defective, 58 MEMS were not returned by the patient or the investigator). There were no statistically significant differences in the distribution of those patients between the intervention and the control group.

Table 1 and Table 2 show the characteristics of physicians and patients, respectively, in the control and intervention groups. All characteristics were similar with the exception that baseline DBP, heart rate, and self-reported medication nonadherence were significantly higher among patients in the intervention group when compared with control group patients.

The mean duration of patient follow-up was 39 months, and 67% of the patients had at least 36 months of follow-up. The ICCs for the outcomes of interest were as follows: 0.197 for SBP, 0.194 for DBP, 0.107 for adherence, and 0.063 for combined cardiovascular events. Table 3 shows the study results for BP and adherence outcomes in the first 6 months of follow-up. At six months, intervention patients had significantly lower mean SBP (148.9 mmHg vs. 151.1 mmHg;  $P=0.008$ ) and lower mean DBP (81.9 mmHg vs. 83.0 mmHg;

P=0.013) when compared with control patients. Moreover, intervention patients were less likely to have an uncontrolled SBP (i.e.,  $\geq 140$ mmHg) when compared with control patients (OR 0.62; 95% CI 0.50, 0.78). On the other hand, intervention patients were not less likely to have an uncontrolled DBP (i.e.,  $\geq 90$ mmHg) when compared with control patients (OR 0.94; 95% CI 0.73, 1.20). Differences around 2mm of Hg in SBP between groups persisted over the 5-years of follow-up, whereas differences in DBP between groups were  $< 1$ mmHg after 18 months of follow-up (Figure 2). Only a few of the SBP differences after the 6-month visit were statistically significant.

Patients in the intervention group also appeared to be more adherent over the six months of the intervention, as they took their correct dose on a greater proportion of days when compared with patients in the control group (92.2% vs. 89.0%, respectively; P=0.002) and were more likely to be at least 80% adherent (OR 1.91; 95% CI 1.19, 3.05) (Table 3). For the other adherence measures, intervention patients were also more likely to achieve a value  $\geq 80\%$  adherence over the six-month period. Expanded Tables 1, 2, and 3 and additional methods descriptions are available on-line.

During the study it was discovered that the MEMS chips of 45 containers malfunctioned at least once in the study, resulting in inflated measurements of between 4–8 uses per day. The malfunctioning MEMS containers were replaced by the manufacturer who also developed an algorithm to identify and delete invalid readings. Through this algorithm we estimated that approximately 5% of all readings on the defective devices were invalid. As a sensitivity analysis, we repeated the analysis excluding the 45 patients who had defective devices and the results did not change (data not shown).

After five years of follow-up, 153 patients had at least one of the composite cardiovascular events - 67 (16%) in the intervention group and 86 (19%) in the control group (Figure 3). Although intervention patients had fewer events when compared with control patients, after adjusting for DBP, age, gender, self-reported measures of adherence, and cardiovascular risk profile, this difference was not statistically significant (hazard ratio 0.97; 95% CI 0.67,1.39).

## DISCUSSION

This multi-component, low-intensity intervention to improve adherence to antihypertensive medication was effective in improving both BP control and adherence. While the magnitude of the SBP effect appeared small (a difference of 2 mm Hg between groups), one large meta-analysis has suggested that such differences could be associated with a 10% reduction in stroke and a 7% reduction in coronary heart disease mortality.<sup>1</sup>

The strengths of the study include the cluster-randomized design, which avoided study contamination resulting from individual physicians treating patients in both study arms. We also assessed adherence objectively, used valid methods to measure BP, and had adequate power for both the BP and adherence study outcomes. Moreover, our findings are consistent with the findings of other recent studies. For example, a smaller study by Qureshi et al.<sup>25</sup> tested a physician-targeted educational intervention. The intervention consisted of a day of training, which reviewed the seventh report of the Joint National Committee (JNC VII) and the report of the Fourth Working Party of the British Hypertension Society modified for the Indo-Asian population. The intervention was effective at improving patient adherence when compared to the usual care groups (48% vs. 32%, respectively;  $p<0.05$ ). Adherent patients experienced greater decreases in SBP when compared with non-adherent patients ( $P<0.05$ ), but the differences were not statistically significant for DBP. Another study by Ogedegbe et al.<sup>26</sup> tested an intervention consisting of motivational interviewing sessions every three months (x4) targeting medication adherence behavior among low-income African-American



women with uncontrolled BP. In that study, baseline adherence was measured with MEMS during a 3-month run-in period, and patients were followed afterward for an additional 9 months. The intervention was associated with a nearly 20% absolute increase in adherence levels at 12 months, but not with statistically significant changes in BP. Blood pressure decreased in both groups, but the study did not report results on the association between adherence levels and BP control.

The fact that mean adherence was close to 90% in both groups in our study could suggest a Hawthorne effect on both groups, whereby patients knowing that their adherence was being monitored changed their behavior accordingly. Periods longer than 6-months might be required to observe a significant attenuation of the Hawthorne effect.<sup>27–29</sup> Although we hypothesized that counting pills could promote a Hawthorne effect in the intervention group, the MEMS bottles may also have resulted in a Hawthorne effect in both study arms, resulting in smaller than expected differences in adherence between groups. On the other hand, high antihypertensive medication adherence rates have also been found in studies measuring adherence with pharmacy refill methods, thus indicating that high levels of adherence might not always be attributable to the Hawthorne effect.<sup>30</sup> Regardless of whether there was a Hawthorne effect, we found clinically and statistically significant differences between the intervention and control groups in our study outcomes.

We did not, however, observe a direct association between adherence and blood pressure control (data not shown). Therefore, it is possible that the study intervention improved BP control through mechanisms other than improved adherence. For example, the intervention may have helped overcome clinical inertia (i.e., clinicians' reluctance to intensify therapy), resulting in better overall BP control.<sup>31</sup> However, changes in BP medication were not allowed by protocol until the third month of follow-up, suggesting that BP improvements were not the result of overcoming clinical inertia. Although other factors may account for the BP improvement, we were likely underpowered to detect the association between adherence and BP control due to the overall high levels of adherence in both groups with limited variability.<sup>15;32;33</sup> In addition, approximately 37% of the patients were using at least one antihypertensive medication for which adherence was not monitored electronically. Perhaps with the additional assessment of adherence for these medications we would have seen a stronger association between adherence and blood pressure control.

This study has additional limitations. As mentioned previously, we had a problem with some of the MEMS containers resulting in invalid readings. However, including or excluding data from the affected participants did not substantively influence our findings. Next, although we instructed physicians to keep a log of how many patients were offered enrollment in the study, many physicians did not complete these logs. Therefore, we are unable to comment on how our study population differed from the larger, eligible patient population. A similar situation occurs with the physicians. An important proportion withdrew without recruiting patients and no information is available on them. Thus, we have a limitation to evaluate the generalizability of our results to the larger population of both patients and physicians. On the other hand, patients included met the eligibility criteria of high cardiovascular risk and complete clinical information was available at baseline. Information on participating physicians was also available from the physicians survey. Finally, adherence is not the only reason explaining poor rates of BP control. As mentioned above, clinician factors, such as clinical inertia, may also play an important role in the unsatisfactory rates of BP control.<sup>31</sup> Therefore, future studies should assess and address both patient adherence and the need for a provider intensification of antihypertensive medication simultaneously. Future studies will also be needed to elucidate the impact of this type of intervention on cardiovascular morbidity and mortality, as this study was underpowered for those outcomes.

In summary, we conclude that a multi-factorial intervention to improve adherence to antihypertensive medication was effective in improving both adherence and BP control. While the effect size was small, we did observe very high levels of adherence in both arms. This suggests that in addition to the intervention described, other factors, such as the Hawthorne effect may have contributed to these results. The relative importance of various components of this intervention, including a potential Hawthorne effect, in improving adherence and BP control has yet to be determined.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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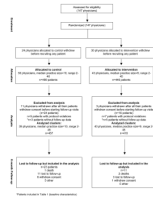
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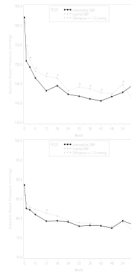


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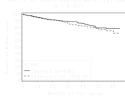
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**Figure 1.** Flow of patients and physicians during recruitment and the first 6 months of follow-up.\*Patients also included in table 1 (Baseline characteristics).



**Figure 2.** Systolic and diastolic blood pressure differences between the intervention and the control group during the 60 months follow-up. Asterisks mark the visits in which differences in BP favoring the intervention group were of 1.5 mm of Hg or more.



**Figure 3.**

Kaplan-Meier survival curve for cardiovascular end-points comparing the intervention and the control groups (log-rank test,  $P = 0.351$ ). The plot shows unadjusted results. Survival results after adjusting, using a multivariable survival Cox model accounting for physician cluster effects, for diastolic blood pressure, age, gender, self-reported measures of adherence, and cardiovascular risk profile, were not statistically significant either (HR 0.97; 95% CI 0.67, 1.39)

**Table 1**

Distribution of physician related characteristics in control and intervention groups. Numbers are mean  $\pm$  SD[N], and N (%).

Variable	Control group (39, 36 physicians with survey data)	Intervention group (40, 33 physicians with survey data)	P value
<u>Variables with data available for all 79 analyzed physicians</u>			
Physicians under the coordination of the Catalan coordinating center	21/39 (53.8%)	22/40 (55.0%)	0.918
Female sex	18/39 (46.2%)	15/40 (37.5%)	0.498
Working place			
Hospital	12/39 (30.8%)	13/40 (32.5%)	
Primary care center	27/39 (69.2%)	27/40 (67.5%)	0.869
Average number of patients per physician	11.8 $\pm$ 8.3 [39]	10.6 $\pm$ 7.9 [40]	0.529
<u>Variables with data available only for the 69 physicians who completed the survey*</u>			
MD degree year	1982.9 $\pm$ 5.3 [35]	1982.8 $\pm$ 6.4 [33]	0.834
Age	43.1 $\pm$ 5.2 [35]	43.6 $\pm$ 6.5 [33]	0.749
Working in a Teaching Center	21/36 (58.3%)	20/33 (60.6%)	0.848
Previous participation in clinical trials	28/35 (80%)	25/33 (75.8%)	0.773
Specialty			
Internal medicine	6/34 (17.6%)	7/33 (21.2%)	
Family medicine	22/34 (64.7%)	19/33 (57.6%)	
Nephrology	6/34 (17.6%)	7/33 (21.2%)	0.836
Practice size in primary care centers (number of patients)	1629.8 $\pm$ 490.3 [24]	1745.5 $\pm$ 493.3 [22]	0.930
Hours a week with direct contact with patients	28.6 $\pm$ 8.5 [35]	27.4 $\pm$ 9.0 [31]	0.649
Average visit time in primary care centers (in minutes)	7.5 $\pm$ 3.2	7.0 $\pm$ 2.2	0.755
Average time visit for follow-up visits in hospital (in minutes)	15.0 $\pm$ 4.4	16.25 $\pm$ 5.3	0.722
Holding a full time job in the health center	27/36 (75.0%)	23/33 (69.7%)	0.788

\* Of 79 physicians who actively recruit patients, 69 (87%) completed the survey



**Table 2**

Distribution of patient related characteristics in control and intervention groups. Numbers are mean  $\pm$  SD[N], and Ns (%).

Variable	Control group (N= 460)	Intervention group (N= 423)	P value
Geographical area			0.943
Madrid coordinating center	154 (33%)	140 (33%)	
Barcelona coordinating center	306 (67%)	283 (67%)	
Baseline SBP	160.8 $\pm$ 15.0 [460]	162.1 $\pm$ 16.3 [423]	0.222
Baseline DBP	86.1 $\pm$ 9.8 [460]	88.6 $\pm$ 11.1 [423]	<0.001
Baseline heart rate	74.3 $\pm$ 12.0 [459]	76.2 $\pm$ 11.6 [421]	0.016
Baseline SBP $\geq$ 140	441/460 (96%)	398/423 (94%)	0.228
Baseline DBP $\geq$ 90	146/460 (32%)	193/423 (46%)	<0.001
Severe hypertension	90/460 (20%)	103/423 (24%)	0.086
Age	66.8 $\pm$ 8.6 [459]	66.3 $\pm$ 8.1 [422]	0.391
Male gender	237/460 (52%)	199/422 (47%)	0.195
BMI>30	221/456 (48%)	220/422 (52%)	0.277
Current smoker	62/458 (14%)	62/422 (15%)	0.623
History of smoking	122/375 (32%)	104/339 (31%)	0.553
HT duration (years)	10.5 $\pm$ 8.7 [460]	11.0 $\pm$ 9.3 [420]	0.454
Number of hypotensive drugs at baseline	2.24 $\pm$ 1.10 [460]	2.20 $\pm$ 1.06 [423]	0.670
Number of hypotensive drugs grouped			
0	2 (0.4)	2 (0.5)	
1	137 (29.8)	125 (29.6)	
2	147 (32.0)	138 (32.6)	
3-4	164 (35.7)	150 (35.5)	
>4	10 (2.2)	8 (1.9)	0.998
Number of drugs adherence was monitored with MEMS system	1.24 $\pm$ 0.43 [458]	1.28 $\pm$ 0.45 [420]	0.196
Patients with combinations of two drugs adherence being monitored with MEMS system	109/458 (23.8%)	116/420 (27.6%)	0.195
Percentage of total number of drugs monitored with MEMS system	66.2 $\pm$ 29.4 [457]	67.9 $\pm$ 28.7 [420]	0.295
Number of risk factors	1.9 $\pm$ 1.2 [460]	1.8 $\pm$ 1.1 [423]	0.769
Left ventricular hypertrophy	128/460 (28%)	120/422 (28%)	0.840
Consumption of alcohol (grs)	40.4 $\pm$ 117.3 [460]	35.2 $\pm$ 86.6 [422]	0.447
Diabetes	289/460 (63%)	266/422 (63%)	0.949
Severe hypertensive retinopathy (III-IV)	12/460 (3%)	11/422 (3%)	0.998
Peripheral arteriopathy	33/460 (7%)	23/422 (5%)	0.294
Stroke history	58/460 (13%)	60/422 (14%)	0.467
Coronary heart disease	43/460 (9%)	43/422 (10%)	0.674
Congestive heart failure	20/460 (4%)	12/422 (3%)	0.233
Proteinuria	57/460 (12%)	46/422 (11%)	0.491
Abnormal creatinine	44/460 (10%)	35/422 (8%)	0.509
Self-reported nonadherence (Haynes-Sackett test) <sup>24</sup>	142/456 (31%)	162/414 (39%)	0.014

Variable	Control group (N= 460)	Intervention group (N= 423)	P value
History of not attending scheduled visits in the previous 6 months* (self-reported) <sup>24</sup>	123/415 (30%)	95/383 (25%)	0.126

\* Patients without visits in the previous 6 months were coded missing.

Table 3

Comparison of blood pressure and adherence outcomes between the control and the intervention group during the first 6 months of follow-up.

Repeated BP Measures (1, 3 & 6 Months visits)*	Unadjusted Analysis		Adjusted analysis	
	Intervention (n=418)	Control (n=457)	Intervention (n=417)	Control (n=453)
SBP mmHg [mean (SE)]	149.7 (0.82)	151.1 (0.70)	148.9 (0.69) <sup>‡</sup>	151.1 (0.57)
Uncontrolled SBP >= 140 mmHg (%)	65.6 <sup>‡</sup>	73.3	66.6 <sup>§</sup>	76.3
Uncontrolled SBP >= 140 mmHg [OR (95% CI)]	0.70 (0.56, 0.87)	1.00 (Ref. group)	0.62 (0.50, 0.78)	1.00 (Ref. group)
DBP mmHg [mean (SE)]	82.8 (0.49)	82.3 (0.42)	81.9 (0.35)//	83.0 (0.30)
Uncontrolled DBP >= 90 mmHg (%)	26.1	22.4	18.1	19.0
Uncontrolled DBP >= 90 mmHg [OR (95% CI)]	1.22 (0.97, 1.55)	1.00 (Ref. group)	0.94 (0.73, 1.20)	1.00 (Ref. group)
6 Month Cumulative main Adherence Outcomes <sup>‡</sup>	Intervention (n=374)	Control (n=423)	Intervention (n=332)	Control (n=377)
Adherence, % days correct dose taken [mean (SE)]	91.2 (0.11)//	88.2 (0.09)	92.2 (0.09) <sup>‡</sup>	89.0 (0.07)
Adherence, % of patients with at least 80% adherence	88.2	83.5	91.9 <sup>‡</sup>	85.6
Adherence ≥ 80% [OR (95% CI)]	1.49 (0.87, 2.54)	1.00 (Ref. group)	1.91 (1.19, 3.05)	1.00 (Ref. group)

\* Analysis for BP outcomes were adjusted for geographic area (Catalonia versus Madrid), number of risk factors, body mass index, age, and the baseline level of the outcome variable.

<sup>‡</sup> Analysis for adherence outcomes were adjusted for baseline diastolic blood pressure, geographic area, self-reported measure of adherence at baseline, self-reported measure of not showing up at the scheduled doctor visits.

<sup>‡</sup> P<0.01

<sup>§</sup> P<0.0001

// P<0.05