Use of Electronic Pill Boxes to Assess Risk of Poor Treatment Compliance
Results of a Large-Scale Trial
Laurent Vaur, Bernard Vaisse, Nathalie Genes, François Elkik, Catherine Legrand, and Louis Poggi

The objective of the present study was to determine the predictive factors of treatment compliance in hypertensive patients. This was an open large-scale multicenter study where mild to moderate essential hypertensive patients received trandolapril (2 mg) once daily for 30 to 60 days in addition to their usual treatment. Trandolapril was packed in electronic pill boxes that registered date and time of each opening. The main compliance parameters were the percentage of missed doses, the percentage of delayed doses, and the percentage of correct dosing periods. Predictive factors of poor compliance (correct dosing periods <80%) were determined using a multivariate stepwise logistic regression analysis. Two thousand one hundred seventy-three patients aged 60 ± 12 years were analyzed. Of the total patients 37% were poor compliers; 29% of patients forgot more than 10% of doses and 36% of patients delayed more than 10% of doses. Ranked predictive factors of poor compliance were: age <60 years (odds ratio [OR], 1.80 [1.49 to 2.17], P = .0001), the Paris area (OR, 1.70 [1.32 to 2.19], P = .0001), smokers (OR, 1.65 [1.29 to 2.11], P = .0001), monotherapy (OR, 1.40 [1.14 to 1.72], P = .0012), and baseline diastolic blood pressure ≥100 mm Hg (OR, 1.21 [1.01 to 1.46], P = .044). Therefore, we conclude that young hypertensives, large city dwellers, and smokers are more likely to be poor compliers. The presence of some of these characteristics might incite the physician either to encourage patient compliance or to prescribe antihypertensive drugs that have an effect that persists even beyond 24 h. Am J Hypertens 1999; 12:374–380 © 1999 American Journal of Hypertension, Ltd.

KEY WORDS: Compliance, risk factors, electronic pill box, angiotensin converting enzyme inhibitor.
The MACH 2 study is a part of the French MACH (Medication event monitoring system for the Assessment of the Compliance of Hypertensives) research program. The MACH 1 study aimed at evaluating the antihypertensive efficacy of a drug in relation to the time interval between taking the final dose and measuring the blood pressure (BP); it was also designed to assess the 1-month compliance of a drug prescribed in monotherapy.

The aim of the present study was to determine the predictive factors of treatment compliance in hypertensive patients. The antihypertensive drug chosen to perform this study, trandolapril, is a once-a-day angiotensin converting enzyme (ACE) inhibitor marketed in most countries.

METHODS

Patients Patients aged 18 years or more with essential hypertension (office sphygmomanometer diastolic BP ≥95 mm Hg) were eligible to enter the study. The main exclusion criteria were any serious chronic disease, known hypersensitivity or contraindication to ACE inhibitors, and impaired renal function. All patients gave their written informed consent. The protocol was approved by the Comité Consultatif de Protection des Personnes se Prêtant a la Recherche Biomédicale of Marseille, France (ethics committee).

Study Design An open large-scale multicenter study was carried out, with each patient receiving trandolapril, 2 mg, once daily for 30 to 60 days. The patients were recommended to take their medication at 8 AM. Trandolapril was either prescribed as a monotherapy in newly diagnosed or not previously treated patients, or added to previous antihypertensive drugs.

Measurement of Compliance Trandolapril was packed in electronic pill boxes (Medication Event Monitoring System [MEMS], Aprex Corp., Fremont, CA). A microprocessor included in the lid registered the date, time, and duration of each opening. The patients were informed of its presence and purpose. At the end of the study, all data recorded by the microprocessor were collected and analyzed using the SAS software (SAS Institute Inc., Cary, NC). For each patient, all calculations were derived from the date and the time of each opening. Each opening was considered as being a single dose intake.

Four quantitative variables were used to assess individual compliance: the percentage of missed doses, the percentage of delayed doses, the percentage of multiple dosing periods, and the percentage of incorrect dosing periods. A missed dose was defined by the absence of recorded opening during one 24-h dosing period (2:00 AM to 1:59 AM). A dose was defined as delayed when: 1) the box was opened more than 25 h after the preceding opening, and 2) these two openings occurred during 2 consecutive days. An overdosing period was defined as a 24-h dosing period (2:00 AM to 1:59 AM) with more than one opening. A dosing period was considered incorrect when including either a missed dose, or a delayed dose, or multiple doses. All these variables were expressed as percentage of prescribed doses.

Blood Pressure Measurements Mercury sphygmomanometer office BP was recorded both at the beginning of the study and at the end of the active treatment period. Physicians were recommended to perform three consecutive measurements with the patient in the sitting position, after a 5-min rest. The three readings were averaged for analysis.

Statistical Analysis Statistical analysis was computed using SAS software. Qualitative variables were expressed as percentages. Quantitative data were expressed in terms of mean ± standard deviation. Because compliance data did not follow a normal distribution, they were expressed by their median, 75th and 95th percentile (5th and 25th percentile were not presented as it added little information).

To determine the factors that might influence treatment compliance, multivariate stepwise logistic regression analyses were carried out taking into account demographics (age, gender, body mass index), clinical baseline characteristics (hypertension duration, BP level, diabetes mellitus, dyslipidemia, smoking habits, coronary artery disease, number of current drugs), family status (married, divorced, single, widow), professional status (working, retired, invalid, unemployed, nonworking), geographic area (northwest, northeast, Paris region, center, southwest, and southeast), and living conditions (country, town). Variables with P < .10 were kept in the final model. Odds ratios and their 95% confidence intervals were used to describe the predictive value of each relevant variable.

RESULTS

Baseline Characteristics A total of 2340 patients entered the study. One hundred sixty-seven patients were excluded from compliance analysis due to premature withdrawal from the study (79 patients), failure to use or to return the electronic pill box (54 patients), technical defect of the electronic pill box (20 patients), lost to follow-up (9 patients), or other major protocol deviations (5 patients). A total of 2173 patients (50.1% men) aged 60 ± 12 years were analyzed. Median hypertension duration was 28 months. Baseline systolic BP to diastolic BP level was 169 ± 14/101 ± 6 mm Hg. The prevalence of cardiovascular risk factors was as follows: diabetes mellitus, 10.4%; overweight, 23.8%; dyslipidemia, 31.7%; and current smokers, 16.0%. Trandolapril 2 mg once daily was given in monotherapy in 1460 patients (67%) not pre-
viously treated. It was added to another antihypertensive drug in 535 patients (25%) and to at least two other antihypertensive drugs in 178 patients (8%).

Assessment of Daily Compliance by Electronic Pill Boxes The mean treatment duration was 49 ± 17 days. Compliance variables are expressed by their median (75th and 95th percentiles). On average, the patients missed 3.4% (11.8% and 39.0%) of doses and median (75th and 95th percentiles). On average, the patients had 6.9% (13.2% and 22.4%) of the doses delayed and 36% of patients delayed >10% of doses. Overdosing periods were very infrequent. Finally, the percentage of incorrect dosing periods during the study was 14.6% (27.3% and 52.4%); this means that the average daily compliance was 85.4%. Thirty-seven percent of patients presented more than 20% of incorrect dosing periods and were defined as poor compliers.

Predictive Factors of Treatment Compliance Results of the univariate and the multivariate analyses are shown in Tables 1 and 2, respectively.

### Table 1. Predictors of Compliance: Results of the Univariate Analysis

<table>
<thead>
<tr>
<th>Explanatory Variable</th>
<th>Delayed Doses ≥10%</th>
<th>Missed Doses ≥10%</th>
<th>Uncorrect Dosing Periods ≥20%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of Patients</td>
<td>P</td>
<td>% of Patients</td>
</tr>
<tr>
<td>Age (&lt;60 v ≥60 years)</td>
<td>50.4 v 25.5</td>
<td>&lt;.001</td>
<td>31.8 v 25.7</td>
</tr>
<tr>
<td>Gender (male v female)</td>
<td>40.6 v 32.1</td>
<td>&lt;.001</td>
<td>30.1 v 26.9</td>
</tr>
<tr>
<td>Hypertension duration (&lt;29 v ≥29 months)</td>
<td>39.4 v 33.1</td>
<td>.001</td>
<td>31.6 v 25.4</td>
</tr>
<tr>
<td>Baseline BP level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(DBP &lt;100 v ≥100 mm Hg)</td>
<td>40.4 v 33.1</td>
<td>.001</td>
<td>31.6 v 25.4</td>
</tr>
<tr>
<td>Monotherapy v polytherapy (all drugs)</td>
<td>39.5 v 29.9</td>
<td>&lt;.001</td>
<td>30.3 v 25.0</td>
</tr>
<tr>
<td>Smoking habit (current smoker v nonsmoker)</td>
<td>46.6 v 34.4</td>
<td>&lt;.001</td>
<td>37.1 v 26.9</td>
</tr>
<tr>
<td>Professional status (active v retired)</td>
<td>45.7 v 25.6</td>
<td>&lt;.001</td>
<td>31.1 v 25.6</td>
</tr>
<tr>
<td>Habitation (town v country)</td>
<td>38.1 v 34.6</td>
<td>NS</td>
<td>30.8 v 26.3</td>
</tr>
<tr>
<td>Geographic area (Paris v provinces)</td>
<td>47.7 v 34.4</td>
<td>&lt;.001</td>
<td>35.8 v 27.4</td>
</tr>
</tbody>
</table>

Age  Patient compliance increased regularly with age as shown in Figure 1. Younger patients (aged <60 years) were more likely to forget more than 10% of doses (31.8% v 25.7%, P = .002) as well as to delay more than 10% of doses (48.8% v 25.5%, P < .001). Consequently, younger patients were more often poor compliers than older patients (45.2% v 29.2%, P < .001). The multivariate analyses showed that age was the first independent predictor of treatment compliance as far as delayed doses and incorrect dosing periods are concerned. An age <60 years multiplied by 1.8 the risk of poor compliance (P = .0001).

Gender  Men were more susceptible to delaying doses than women (40.6% v 32.1%, P < .001). Forgetters were also more often men, but the difference did not reach statistical significance. According to the univariate analysis, 39.4% of men were poor compliers compared to 33.9% of women (P = .007). However, when adjusted for other variables, in particular age, gender was no longer a predictor of incorrect dosing periods,
but only an independent predictor of delayed and missed doses.

Hypertension Duration  Both forgetters and delayers were more often found in recently diagnosed patients (hypertension duration, <29 months). Among recently diagnosed hypertensives, 39.9% of patients were poor compliers compared to 33.1% of older hypertensives ($P = .001$). However, this difference disappeared when adjusted for age. The only independent link was that found for missed doses.

Number of Antihypertensive Drugs  As shown in Table 1, the number of missed and delayed doses was reduced in patients receiving several antihypertensive drugs compared to patients receiving monotherapy. These differences remained statistically significant for delayed doses and incorrect dosing periods after adjustment for other relevant variables as shown in Table 2. In fact this variable was strongly related to hypertension duration (Table 3), and in the multivariate analyses, variables kept in each of the three final models (delayed doses, missed doses, and incorrect dosing periods) included either monotherapy or hypertension duration but never both. Indeed, the choice between these two variables was very sharp and as one was included in the model, the other one was no longer relevant.

Baseline Blood Pressure  Patients with baseline diastolic BP $\geq$100 mm Hg were more often poor compliers (38.8% v 33.6%, $P = .012$). This holds true after adjustment for other relevant variables (odds ratio, 1.21, $P = .044$).

### Table 3. Baseline Characteristics Linked to the Prescription of Several Antihypertensive Drugs

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients With Several Antihypertensives ($n = 713$)</td>
<td>$P$</td>
<td>$X^2$ Value</td>
</tr>
<tr>
<td>Longer hypertension duration</td>
<td>77%</td>
<td>$&lt;.001$</td>
</tr>
<tr>
<td>Retirement</td>
<td>56%</td>
<td>$&lt;.001$</td>
</tr>
<tr>
<td>Elderly</td>
<td>65%</td>
<td>$&lt;.001$</td>
</tr>
<tr>
<td>Male gender</td>
<td>50%</td>
<td>NS</td>
</tr>
</tbody>
</table>

The link between baseline characteristics and number of prescribed antihypertensives was searched using: 1) a univariate analysis that indicates the percentage of patients presenting the considered baseline characteristic among the patients receiving several antihypertensive drugs; and 2) a multivariate regression logistic analysis (parameters with $P < .10$ are presented).
TABLE 4. ANTIHYPERTENSIVE EFFICACY ACCORDING TO PATIENT’S COMPLIANCE

<table>
<thead>
<tr>
<th>Compliance (% of correct dosing periods)</th>
<th>0–49%</th>
<th>50–79%</th>
<th>80–100%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong> SBP decrease (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20.9 ± 13.1</td>
<td>23.2 ± 13.6</td>
<td>23.0 ± 14.5</td>
<td>.25</td>
<td></td>
</tr>
<tr>
<td>14.4 ± 9.1</td>
<td>16.0 ± 8.5</td>
<td>16.0 ± 8.1</td>
<td>.12</td>
<td></td>
</tr>
<tr>
<td>Normalized patients (%)</td>
<td>71.7</td>
<td>81.5</td>
<td>84.7</td>
<td>.002</td>
</tr>
</tbody>
</table>

**Smoking Habits** Current smokers forgot more doses (37.1% vs 26.9%, P < .001) and delayed more doses (46.6% vs 34.4%, P < .001) compared to nonsmokers. Consequently, poor compliers were more frequent in current smokers (49.4% vs 34.2%, P < .001). Smoking status was the first independent predictive factor of missed doses. However, it was no longer a predictor of delayed doses after adjustment for age and geographic area. Overall, it remained an independent predictor of poor compliance (odds ratio, 1.65, P = .0001).

**Family Status, Professional Status, and Living Conditions** There was no link between family status and compliance. In addition, the apparent link between professional status or living conditions (country or town) and compliance was mostly attributable to confounding variables. After adjustment, the single relevant parameter was patient’s retirement. Even when adjusted for age, retired patients were less likely to either delay (P = .0005) or miss doses (P = .044).

**Geographic Area** The higher prevalence of poor compliers was found in the Paris area (48.9%). In the multivariate analyses, living in the Paris area was a strong independent predictor of poor compliance. It increased by about 50% (see odds ratios in Table 2) the number of patients exhibiting delayed doses, missed doses, and incorrect dosing periods.

**Relationship Between Treatment Compliance and Antihypertensive Efficacy** Treatment efficacy and its relation to compliance was investigated in 2051 patients. Of the 2173 patients analyzed for compliance, 92 were excluded because their initial diastolic BP was <90 mm Hg, 18 because of unauthorized modification of antihypertensive treatment during the course of the study, and 12 because BP measurements were not correctly performed. Mean blood pressure decreased by 23.0 ± 14 mm Hg for systolic BP (P = .0001) and by 15.9 ± 8 mm Hg for diastolic BP (P = .0001). Eighty-three percent of patients were normalized (diastolic BP ≤ 90 mm Hg). Antihypertensive effects were compared in the three groups of patients categorized according to their compliance (Table 4). Efficacy tended to be greater as compliance increased. However, this trend was only statistically significant regarding percentage of subjects responding to therapy.

**DISCUSSION**

To our knowledge, this is the largest study using electronic pill boxes to evaluate treatment compliance in hypertensive patients. With a simple design it allowed for quantifying the importance of poor compliance in general practice. Our results suggest that about one-third of the patients will present significant compliance violations in the 2 months after the initial prescription of an antihypertensive. This figure is close to that reported in small-sized trials, as well as in the MACH 1 study. However, this proportion is probably underestimated. The fact that patients were told of the purpose of the electronic pill box may have enhanced treatment compliance. Furthermore, participation in a clinical trial may in itself promote better compliance.

The main objective of the MACH 2 study was to individualize factors affecting patient compliance. The large size of the present population as well as the accuracy of the compliance evaluation by electronic pill boxes increased the statistical power of the analysis. Therefore, variables rejected as nonrelevant in our analysis are very unlikely to play a significant role in determining compliance. However, as the study was focused on demographic, clinical, and socioeconomic parameters, behavioral factors that may influence patient compliance were not explored. In addition, as this was a rather short-term study, we cannot extrapolate from our observations the determinants of compliance during chronic treatment.

The role played by age in compliance remains controversial. Some investigators reported that younger patients were noncompliant. However, other researchers found no variation in compliance with age. In the MACH 1 study, younger patients more frequently alter the time at which they take their medication but the number of forgotten doses showed no correlation with the patient’s age. In the present study, patient compliance increased regularly with age. Older patients were less likely to delay or to forget a dose.

As already mentioned in the MACH 1 study, patients from the greater Paris region were poorer compliers than patients living in the provinces. As this relationship holds true after adjustment for other relevant variables, the difference observed in Parisians may be related to differences in lifestyle. The fact that smokers and nonretired patients were poorer compliers suggests that the stress of daily living plays an important role in patients’ compliance.
It is well known that treatment regimens affect patients’ compliance. Indeed, it has been clearly demonstrated that compliance improved from a three or four times daily regimen to a once daily regimen.13–15 Three recent studies using electronic pill boxes have also shown a lower compliance when using twice daily drugs compared to once daily drugs.8,16,17 By extrapolation, it may seem obvious that compliance should be better in patients treated by a single drug rather than several. Our results suggest just the opposite; compliance increased with the number of drugs prescribed. This relationship was, however, weakened when taking into account confounding variables, such as age, which is correlated both to compliance and to the number of prescribed drugs. Furthermore, it should be noted that a high number of prescribed drugs cannot be considered as an independent predictor of compliance without caution, because it is highly correlated to the duration of hypertension (Table 3) and also probably to its severity (not analyzed in our study). Patients taking many drugs have a longer history of hypertension and it may be more severe, which is not without influence on compliance as demonstrated for hypertension duration in Table 1.

Finally, male gender has been sometimes proposed as a potential risk factor for poor compliance.18 In the present study, we found that women were less likely to delay or miss doses. We would rather think that this is more due to women being accustomed to regular medications (oral contraceptives, hormone replacement therapies) than to men being more careless.

In several studies,6,19 treatment efficacy decreased as the percentage of noncompliant patients increased. In the present study, a lower baseline diastolic BP level was associated with a better compliance to trandolapril. This may also be interpreted as a consequence of better treatment compliance during the previous weeks. However, the link between treatment efficacy and compliance was tenuous as shown in Table 4. The percentage of normalized patients was the only criterion significantly linked to compliance (and may be by chance alone). This can be explained by the following: 1) because this is an uncontrolled study measuring BP with a mercury sphygmomanometer, the accuracy of the BP response measurement can be questioned; 2) the efficacy evaluation took place at a single time point, whereas compliance was recorded daily during several weeks; and 3) the long duration of action of trandolapril probably attenuated the effects of occasionally missed doses.20,21

In conclusion, in asymptomatic chronic diseases, such as hypertension, the rate of treatment compliance is frequently low.19 In this 2-month large-scale trial, 37% of patients were poor compliers. Given the clear evidence that reducing BP decreases the cardiovascular complications of hypertension, loss of efficacy represents the principal risk of noncompliance.22 In this context, defining predictors of patient compliance may help the physician in the therapeutic approach. Our study found that patients aged <60 years, large city dwellers (Parisians), smokers, and recently diagnosed hypertensives were more likely to be poor compliers. Such risk factors should incite the physician either to actively encourage patient compliance19,23 or to prescribe longer acting antihypertensive agents that remain active even in cases of delayed or even missed doses.24,25

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