

Participation in a Clinical Trial Enhances Adherence and Persistence to Treatment : A Retrospective Cohort Study

Hein A.W. van Onzenoort, Frederique E. Menger, Cees Neef, Willem J. Verberk, Abraham A. Kroon, Peter W. de Leeuw and Paul-Hugo M. van der Kuy

Hypertension. 2011;58:573-578; originally published online August 8, 2011;

doi: 10.1161/HYPERTENSIONAHA.111.171074

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.

Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://hyper.ahajournals.org/content/58/4/573>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Hypertension* is online at:
<http://hyper.ahajournals.org/subscriptions/>

Participation in a Clinical Trial Enhances Adherence and Persistence to Treatment

A Retrospective Cohort Study

Hein A.W. van Onzenoort, Frederique E. Menger, Cees Neef, Willem J. Verberk, Abraham A. Kroon, Peter W. de Leeuw, Paul-Hugo M. van der Kuy

Abstract—Poor adherence to treatment is one of the major determinants of an uncontrolled blood pressure. Participation in a clinical trial may increase patient's adherence to treatment. This prompted us to investigate adherence and persistence profiles in patients with hypertension who had participated in a clinical trial, by collecting pharmacy refill data before, during, and after participation in the trial. Pharmacy refill data of 182 patients with hypertension who participated in the Home Versus Office Blood Pressure Measurements: Reduction of Unnecessary Treatment Study between 2001 and 2005 were obtained from 1999 until 2010. Refill adherence to treatment was compared for the periods before, during, and after this trial. Persistence to medication was investigated for the period after termination of the trial. Refill data were available for 22 600 prescriptions. Participation into the trial significantly increased refill adherence, from 90.6% to 95.6% ($P<0.001$). After the trial period, refill adherence decreased again to 91.8% ($P<0.001$), which did not differ from the adherence before the start of the trial ($P=0.45$). Except for adherence to trial medication, adherence to nontrial-related drugs also increased as a consequence of trial participation, from 77.6% to 89.6% ($P<0.001$). After termination of the trial, median persistence was 1424 days. Participants classified as adherent (adherence: $>90\%$) were less likely to discontinue treatment compared with nonadherent participants (odds ratio: 0.66 [95% CI: 0.45 to 0.98]). Participation in a clinical trial significantly increases adherence to both trial-related and nontrial-related treatment, suggesting that participants in a trial are more involved with their conditions and treatments. (*Hypertension*. 2011;58:573-578.)

Key Words: medication adherence ■ patient compliance ■ medication persistence ■ hypertension ■ refill adherence

Poor adherence to treatment is one of the major determinants of an uncontrolled blood pressure (BP). According to the World Health Organization, only 50% of the patients with hypertension do take medication as prescribed.¹ Moreover, $\leq 50\%$ of the patients with hypertension discontinue treatment within 1 year after initiation.²⁻⁵

Despite these alarming figures, several observations indicate that adherence to treatment is fairly high in patients who participate in a clinical trial.⁶ So, there seems to exist a difference in adherence rates between “real-life” practice and clinical practice under experimental conditions,⁷ suggesting that participation in a clinical trial increases adherence, at least to treatment. This positive reinforcement could be explained by the specific design of the study in which patients usually have to attend the clinic more often than usual. Indeed, we demonstrated recently that adherence rates increase significantly before an upcoming visit.⁸ Alternatively, patients who are more engaged with their condition and

treatment may be more willing to participate in a trial in which adherence is monitored. Consequently, patients may be more adherent upfront as compared to what is observed in a general population. All of these considerations may compromise the generalizability of trial-derived adherence results.

For the interpretation of adherence data, it is important to distinguish between 2 important aspects of drug intake behavior, the quality of execution and the degree of continuation of patients' dosing regimen.² The effectiveness and clinical power of pharmacotherapy in chronic diseases depend greatly on the degree of continuation (or persistence). However, when patients are engaged with treatment for a certain period of time, the quality of execution of the dosing regimen determines drug action.

To date, no information is available with respect to the effect of a clinical trial itself on adherence to treatment. This prompted us to investigate adherence and persistence profiles in patients with hypertension who had participated in a

Received February 6, 2011; first decision February 26, 2011; revision accepted July 12, 2011.

From the Department of Clinical Pharmacy (H.A.W.O.), Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; Utrecht Institute for Pharmaceutical Sciences (F.E.M.), Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht, the Netherlands, Department of Clinical Pharmacy and Toxicology (C.N.), University Hospital Maastricht, Maastricht, the Netherlands; Cardiovascular Research Institute Maastricht (C.N., A.A.K., P.W.d.L.), Maastricht University and Department of Internal Medicine, University Hospital Maastricht, Maastricht, the Netherlands; Microlife Corporation (W.J.V.), Taipei, Taiwan; Department of Clinical Pharmacy (P.-H.M.v.d.K.), Orbis Medical Centre, Sittard, the Netherlands.

Correspondence to Hein A.W. van Onzenoort, Radboud University Nijmegen Medical Centre, Department of Clinical Pharmacy, PO Box 9101, 6500 HB Nijmegen, the Netherlands. E-mail H.vanOnzenoort@akf.umcn.nl

© 2011 American Heart Association, Inc.

Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.111.171074

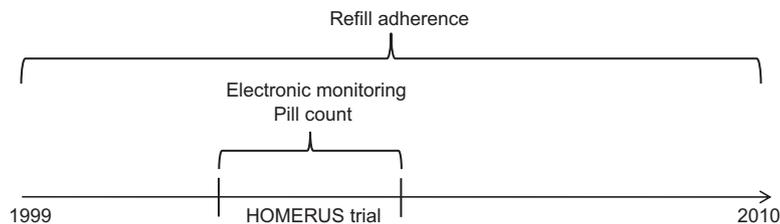


Figure 1. Time frame of adherence measurements.

clinical trial, by collecting refill data before, during, and after participation in the trial. We hypothesized that during the trial adherence would be better as compared with that in the periods before and after the trial. In this analysis, we also included nontrial-related medication and investigated whether a possible increase in adherence during the trial period resulted in better BP control.

Methods

Study Population

We recruited participants who participated in the Home Versus Office Blood Pressure Measurements: Reduction of Unnecessary Treatment Study (HOMERUS)^{9,10} between 2001 and 2005. The HOMERUS was a multicenter, prospective, randomized, double-blind trial with a parallel-group design in which patients aged ≥ 18 years of age and whose office BP was >139 mm Hg systolic and/or 89 mm Hg diastolic were included. Participants were recruited from the outpatient departments of 4 participating university hospitals and affiliated general practices. Both previously treated and untreated patients qualified for inclusion. In all of them, secondary hypertension had been ruled out by laboratory investigation. At entry into the study, any existing antihypertensive therapy was discontinued whenever possible, and participants entered a placebo run-in period of 4 weeks' duration before study treatment was initiated. Study treatment was instituted stepwise based on BP according to the following schedule: (1) step 1, lisinopril 10.0 mg once daily plus 1 tablet of placebo once daily; (2) step 2, lisinopril 20.0 mg once daily plus 1 tablet of placebo once daily; (3) step 3, lisinopril 20.0 mg once daily plus hydrochlorothiazide 12.5 mg; and (4) step 4, lisinopril 20.0 mg once daily plus hydrochlorothiazide 12.5 mg plus amlodipine 5.0 mg.

Atenolol was prescribed to participants intolerant for lisinopril. The goal BP ranged between 120 and 139 mm Hg systolic and between 80 and 89 mm Hg diastolic. In participants who were above the target BP (ie, systolic >139 mm Hg and/or diastolic >89 mm Hg), antihypertensive treatment was intensified by 1 step. If BP was lower than the target (systolic <120 mm Hg and diastolic <80 mm Hg), treatment was reduced by 1 step. All of the drugs were prescribed to be taken in the morning. Participants were followed-up for 7 visits over a period of 1 year.⁹

Adherence Measurement

The total number of participants in the HOMERUS was 470. Of these, 228 participants, recruited by the coordinating center (Maastricht University Hospital) and surrounding general practitioners' practices, were included in the present study. Participants' filled prescriptions from computerized pharmacy systems were obtained from 1999 until 2010 (Figure 1). In the case where patients did not collect their drugs at the same pharmacy department during that period, other pharmacy departments were contacted to retrieve as many data as possible. Accordingly, we collected data for the 2-year period before the trial until 5 years after its completion. During the HOMERUS, proper adherence to antihypertensive medication was concurrently measured by both pill count and Medication Event Monitoring System (MEMS) V TrackCaps (Aardex Corp, Zug, Switzerland). The MEMS-TrackCap is an electronic monitoring system designed to compile the dosing histories of ambulatory participants who are prescribed oral medications.¹¹ Microelectronics integrated into the cap of pill containers record the time and date that

the container is opened or closed. Because this is true for all indirect adherence monitoring systems, MEMS does not register pill consumption.

Filled Prescriptions

Prescription records obtained from the pharmacies included the names of all of the dispensed drugs, the Anatomic Therapeutic Chemical (ATC) classification system, prescribed daily dose, quantity dispensed at each pharmacy fill, and the dates of the prescription fills. A prescription fill covered a 90-day drug intake. We considered participants as continuous users when ≥ 3 consecutive prescriptions were filled. In addition, a gap between 2 consecutive prescriptions of ≤ 90 days after the theoretical duration of the prescription was allowed.¹² Participants who obtained their medications after this allowed treatment gap were considered as noncontinuous users for that specific drug.

Informed Consent

This study was approved by the review board of the University Hospital of Maastricht. Participants gave written informed consent before collection of the prescription records. Of the 228 participants who were invited to participate, 46 declined participation (Figure 2). Consequently, prescription records were obtained from 182 participants. Procedures were followed in accordance with institutional guidelines.

Statistical Analyses

Refill adherence was calculated for each ATC code,¹³ as the theoretical duration divided by the period between the start date and the date of the last prescription filled. The theoretical duration was calculated by dividing the number of units dispensed by the prescribed daily dose. Filled prescriptions in which no daily dose was registered or no theoretical duration could be calculated were excluded from the analysis. Arbitrarily, an adherence level of $\geq 90\%$ was defined as acceptable. Participants with an adherence of $\geq 90\%$ were then classified as adequate adherers, whereas participants with

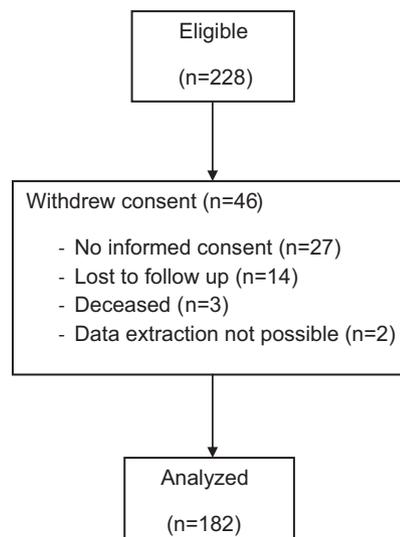


Figure 2. Flow diagram of study subjects.

Table 1. Baseline Characteristics of Patients Participating (n=182) and of Patients Who Declined Participation (n=46)

Characteristic	Participating Patients (n=182)	Not Participating Patients (n=46)
Age, y (SD)	57 (10)	56 (11)
Male, n (%)	93 (51)	19 (41)
Smoking, n (%)	32 (18)*	9 (20)†
Alcohol, n (%)	142 (78)‡	32 (70)‡
Diabetes mellitus, n (%)‡	12 (7)	2 (4)
Time past since diagnosis of hypertension, y (SD)	9.7 (8)	9.0 (6)

*Data missing for 2 participants.

†Data missing for 1 participant.

‡Data missing for 3 participants.

an adherence of <90% were classified as poor adherers. Adherence rates are presented as mean values, including SDs. Differences between the 3 periods (ie, before, during, and after the trial) in adherence rates were analyzed by pairwise comparisons with Bonferroni correction. Risk estimates on BP control were calculated for adherent participants before and throughout the study period. We considered continuation of the HOMERUS medication after the trial period in the case where participants filled these prescriptions within 90 days after termination of the trial. Persistence of these drugs was calculated as the length of time during which medication was taken. We used Kaplan-Meier curves to display persistence over time. To distinguish persistence for the different antihypertensive drugs used, we constructed Kaplan-Meier plots, which were formally tested with a Cox proportional hazards model.

We also analyzed whether adherence rates obtained by pill counts differed between participants whose adherence had been monitored electronically by MEMS and those in whom only pill counts were used. During the clinical trial, adherence rates based on pill counts were calculated both in participants originating from the Maastricht region (n=228) and other centers (n=242), whereas MEMS monitoring was performed only in participants from the Maastricht region. Adherence rates obtained by pill counts were calculated for the aforementioned antihypertensive drugs, which were used in the HOMERUS. Adherence measured by pill counts was calculated as the percentage of the number of prescribed pills corrected for the number of returned pills divided by the period (in days) multiplied by 100%. A *P* value <0.05 was considered to be statistically significant. We used SPSS version 15.0 (SPSS, Inc, Chicago, IL) for all of the statistical analyses.

Results

Altogether, 228 participants who participated in the HOMERUS and whose adherence had been monitored both electronically and by pill count during the trial were eligible for this study. Of these, 46 withdrew or refused consent for various reasons (Figure 2). Consequently, pharmacy refill data from 1999 until 2010 were obtained from 182 participants. Participant baseline characteristics at the time of inclusion into the trial are presented in Table 1. Baseline characteristics of the 46 participants who did not sign informed consent did not differ from those in this study.

Refill data were available for 22 600 prescriptions. The monitored periods covered an average of 993 days (SD: 517 days), 250 days (SD: 71 days), and 1695 days (SD: 475 days), respectively, for the periods before, during, and after the trial. The mean number of drugs prescribed was 3.2, 3.6, and 5.2 for the periods before, during, and after the trial. Participation

Table 2. Effect of a Clinical Trial on Adherence to Treatment

Adherence Measure	Before Trial	During Trial	After Trial	<i>P</i>
Mean adherence, overall, % (SD)	90.6 (11)	95.6 (7)	91.8 (10)	<0.001
Mean adherence, per ATC code, % (SD)				
A	88.5 (17)	90.8 (16)	86.8 (20)	0.59
B	92.8 (9)	89.8 (13)	96.3 (8)	0.025
C	95.1 (9)	97.9 (7)	95.6 (9)	<0.001
G	82.6 (28)	89.7 (20)	93.3 (15)	0.20
H	90.9 (12)	95.5 (7)	87.1 (27)	0.67
L	99.0 (...)	...	84.2 (22)	0.55
M	65.1 (33)	69.0 (36)	69.9 (33)	0.61
N	74.2 (31)	74.9 (32)	76.4 (28)	0.93
R	26.9 (...)	46.6 (...)	84.0 (24)	0.079

ATC indicates Anatomic Therapeutic Chemical; A, alimentary tract and metabolism; B, blood and blood-forming organs; C, cardiovascular system; G, genito-urinary system and sex hormones; H, systemic hormonal preparations, excluding sex hormones and insulins; L, antineoplastic and immunomodulating agents; M, musculo-skeletal system; N, nervous system; R, respiratory system.

into the trial significantly increased refill adherence, from 90.6% to 95.6% (*P*<0.001; Table 2). After the trial period, refill adherence decreased again to 91.8% (*P*<0.001), a level that did not differ from the adherence before the start of the trial (*P*=0.45). When we stratified for cardiovascular (ATC code C) and noncardiovascular drugs (ie, the remaining ATC codes) participation in the clinical trial increased adherence to noncardiovascular treatment, as well from 77.6% to 89.6% (*P*<0.001). After the trial period, refill adherence fell back to 84.1%, which did not differ from the adherence observed before and during the trial period. Differences in adherence to treatment between the periods for each ATC code were only significant for cardiovascular (C) medication and for drugs related to blood and blood-forming organs (B; Table 2). Drugs in the latter category were acetic salicylic acid, folic acid, and ferric salts.

We analyzed whether adherent participants were more likely to achieve BP control (BP <140/90 mm Hg) at the end of the trial period. Before the start of the clinical trial, 139 participants were prescribed cardiovascular medication. Of these, 106 participants (76%) were classified as adherent (adherence >90%) to cardiovascular medication and remained so during the trial period. Despite an adequate adherence level, 63 participants (59%) did not reach BP control during the trial compared with 43 (41%) participants who did (Figure 3). The chance of having a participant's BP controlled under the observation of an adequate adherence level was 0.68 (95% CI: 0.46 to 1.00).

We also analyzed whether the effect of participation in a clinical trial that aimed to study adherence to treatment was confounded by the use of MEMS monitoring. For this analysis we used pill counts derived from the entire HOMERUS population. Mean adherence as determined by pill counts during the trial was comparable in participants whose adherence had been monitored electronically by MEMS and by pill counts together (n=182) and in partici-

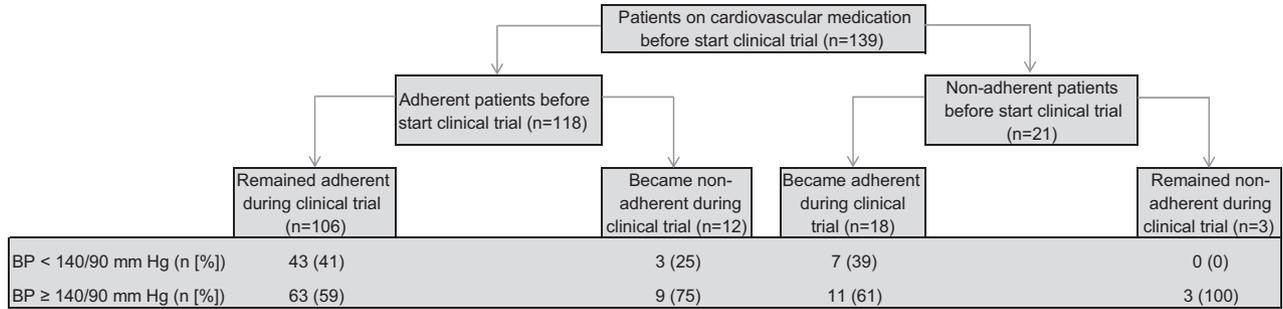


Figure 3. Flow diagram of proportion of adherent and nonadherent participants in relation to blood pressure (BP) control at the end of the clinical trial.

pants whose adherence had been monitored by pill counts only (n=242; 94.0% versus 92.6%; P=0.20).

During the HOMERUS, cardiovascular drugs with ATC codes C03 (hydrochlorothiazide), C07 (atenolol), C08 (amlodipine), and C09 (lisinopril) were prescribed. Before the start of the trial, 57 participants (31%) were using drugs with the same ATC code as was used during the HOMERUS. The mean number of drugs used was 1.4 (SD 0.73). After the trial period, 150 participants (82%) continued using the HOMERUS medication for a mean period of 3.6 years (SD: 1.9). Of the remaining 32 participants, 13 subjects (41%) were switched directly from HOMERUS medication to other antihypertensive drugs, 4 participants (13%) dropped out during the trial, and 1 patient filled the prescription >90 days after termination of the trial. In 9 participants (28%), refill data were not available for the period after the trial, and in 5 participants (16%), antihypertensive medication was no longer indicated based on BP. The mean number of drugs used was 1.9 (SD 0.83). Figure 4 shows a Kaplan-Meier estimate of persistence after the trial period for the HOMERUS drugs. Median duration of continuation was 1424 days after termination of the trial. Persistence decreased during the first 1, 2, and 3 years after termination of the trial to 83%, 74%, and 68%, respectively. No differences in duration of continuation between the different drugs used were observed ($\chi^2=2.21$; P=0.70). Participants who were classified as adherent (adherence >90%) based on refill data showed a longer persis-

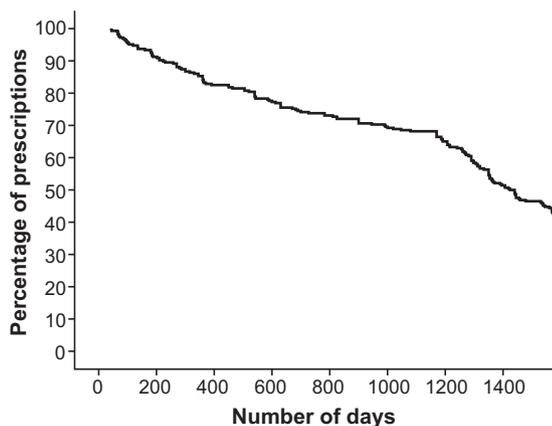


Figure 4. Time course of persistence after the clinical trial of the antihypertensive drugs started during the Home Versus Office Blood Pressure Measurements: Reduction of Unnecessary Treatment Study (HOMERUS).

tence (Figure 5). Median duration of continuation was 1000 days for nonadherent participants as compared with 1440 days for adherent participants. The chance that a patient would discontinue treatment early was 0.66 (odds ratio) for participants classified as adherent (95% CI: 0.45 to 0.98).

Discussion

The results from the present study in patients with hypertension demonstrate that participation in a clinical trial increases adherence to both study and nonstudy medication. In addition, continuation of study medication after termination of the trial seems to persist for a relatively long period.

Early discontinuation of treatment and poor adherence form a major barrier for long-term treatment of hypertension. Indeed, the World Health Organization stated that poor adherence severely compromises the effectiveness of treatment.¹ It is, however, remarkable that adherence levels as found in clinical trials are substantially higher than what is observed in real-life settings.⁶ There are several explanations for the differences in adherence rates, as observed in observational studies and clinical trials. First, the specific study protocol of the clinical trial may motivate patients to follow their prescriptions more accurately. Especially when patients have to visit the clinic more often than usual, white coat

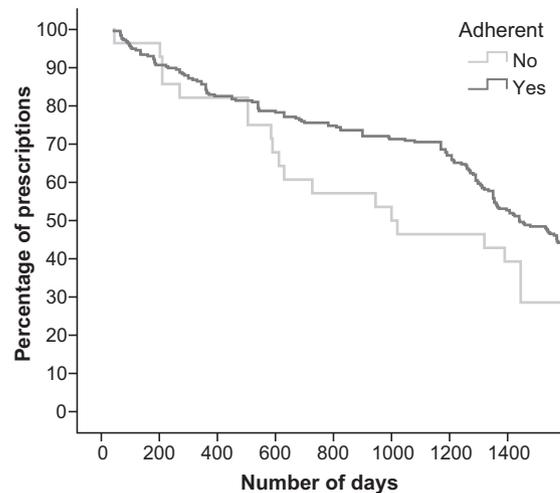


Figure 5. Time course of persistence after the clinical trial of the antihypertensive drugs started during the Home Versus Office Blood Pressure Measurements: Reduction of Unnecessary Treatment Study (HOMERUS) stratified by adherence status (adherent if adherence rate >90%).

adherence may have a positive effect on overall adherence to treatment.⁸ Second, patients who are more concerned about their health and treatment may be more willing to participate in a clinical trial in which adherence is monitored. Finally, patients who are already adherent upfront may be more inclined to participate in a clinical trial. Our study shows that refill adherence before participation in the HOMERUS was already as high as 91%. For cardiovascular drugs, the adherence rate was 95%. These findings support the latter explanation for the difference in adherence rates found between clinical trials and observational studies. Despite the high adherence rate before the HOMERUS, participation resulted in a further increase in adherence. Interestingly, this effect was also observed with noncardiovascular drugs, suggesting that patient perception of illnesses and their treatments are positively influenced by participation in a clinical trial. The relatively long period of continuation of the HOMERUS drugs and the high adherence rate after termination of the clinical trial support this hypothesis.

Poor adherence to treatment is still considered a major determinant of an uncontrolled BP control.^{14–16} The results of our study showed that, despite a high adherence rate before and during the trial, the number of participants with an uncontrolled BP remained fairly high. This suggests that failure to reach BP control using a given drug regimen is not necessarily attributed to a problem of poor adherence to treatment. Treating physicians should be aware of this when being confronted with patients with an uncontrolled BP.

Although several studies have investigated persistence rates of antihypertensive drugs based on refill data,^{3–5} comparing the results is difficult, because studies used different methodologies for calculating persistence rates.¹² Despite these differences, a consistent observation is that persistence decreases rapidly ($\leq 50\%$) within 1 year after initiation of antihypertensive treatment and continues to decrease in the following years. These data emphasize the importance of supporting and motivating patients to adhere to the prescribed treatment, especially in the early phase of treatment. Although our study also indicates that it is difficult for patients to continue the prescribed medication, the fall in persistence during the first year after termination of our trial was only 15%, which is below what is usually observed.^{3–5} This suggests that a positive study effect on persistence to treatment is sustained for a short period of time.

We defined participants as adherent when adherence rates were $\geq 90\%$. Although this degree of adherence is considered fairly high for antihypertensive treatment, participants who were classified as nonadherent were significantly less persistent than those who were classified as adherent. These results underscore the importance of presenting data on adherence not exclusively for the supervised treatment period.²

In this study, we used refill data from computerized pharmacy databases to calculate adherence rates. Refill adherence rates have been used extensively for the assessment of drug acquisition and dispensing. Compared with electronic monitoring, refill data provide researchers with a relatively simple method for investigating exposure to medication in large populations.^{17–19} Moreover, this method is suitable for investigating long-term persistence to treatment and gaps in

medication supply.^{18–20} Therefore, our conclusions are probably valid from a scientific point of view.

The results of our study must be interpreted within the context of its limitations. First of all, an effect of participation in a clinical trial on adherence to treatment may be compromised by the MEMS monitoring, as performed in our population. Several studies show that electronic monitoring increases adherence to treatment.^{21–25} However, most of these studies had followed patients for only a short period of time, making it difficult to predict sustainability of a monitoring effect.^{22–24} In our study, adherence rates based on pill counts were comparable for participants whose adherence had been monitored electronically by MEMS as well as by pill counts and for those in whom adherence had been monitored by pill counts only. These results may suggest that electronic monitoring has a limited effect on adherence to treatment during a trial. Consequently, the effect on adherence may be attributable solely to participation in the trial. Whether this is true for patients who are less adherent than what is observed in our study is not clear. Second, and this is true for all methods of adherence measurement, discarding of drugs is difficult to prove when using refill data. Third, generalizability of the results might be compromised by the specific selection of study subjects. We included participants from a population that had already participated in a clinical trial. The possibility exists that these patients are more inclined to participate in another study than patients who have not participated in a trial yet.

Perspectives

Generalizability of adherence results is an important issue in research. The results of our study underscore the difficulties in interpretation and implications of adherence data into clinical practice. Participants in our study showed high adherence rates upfront and during the trial. Treating physicians should be aware that adherence rates observed in clinical trials do not represent a real-life setting. In addition, selection of highly adherent patients may confound the effectiveness of intervention strategies for improving adherence. Whether improvement in adherence could be more substantial in populations with adherence rates that are lower than the high adherence rates that we observed should be subject to further research. Because these patients are probably less inclined to participate in a trial, it will be a challenge for researchers and physicians to include them into a trial.

Sources of Funding

The Home Versus Office Blood Pressure Measurements: Reduction of Unnecessary Treatment Study was funded by the Netherlands Organization for Health Research and Development (Health Care Efficiency Research Program; grant 945-01-043) and the Dutch Heart Foundation (grant 2005B101).

Disclosures

W.J.V. is an official employee of Microlife Corporation.

References

1. Sabate E. *Adherence to Long Term Therapies: Evidence for Action*. Geneva, Switzerland: World Health Organization; 2003.

2. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. *BMJ*. 2008;336:1114–1117.
3. Van Wijk BL, Shrank WH, Klungel OH, Schneeweiss S, Brookhart MA, Avorn J. A cross-national study of the persistence of antihypertensive medication use in the elderly. *J Hypertens*. 2008;26:145–153.
4. Caro JJ, Salas M, Speekman JL, Raggio G, Jackson JD. Persistence with treatment for hypertension in actual practice. *Can Med Assoc J*. 1999;160:31–37.
5. Bourgault C, Sénécal M, Brisson M, Marentette MA, Grégoire JP. Persistence and discontinuation patterns of antihypertensive therapy among newly treated patients: a population-based study. *J Hum Hypertens*. 2005;19:607–613.
6. Wetzels GE, Nelemans P, Schouten JS, Prins MH. Facts and fictions of poor compliance as a cause of inadequate blood pressure control: a systematic review. *J Hypertens*. 2004;22:1849–1855.
7. Prado JC Jr, Mion D Jr. Adherence to medication: the importance of research in primary care. *Am J Hypertens*. 2010;23:109.
8. Van Onzenoort HA, Verberk WJ, Kroon AA, Kessels AG, Nelemans PJ, van der Kuy PH, Neef C, de Leeuw PW. Effect of self-measurement of blood pressure on adherence to treatment in patients with mild to moderate hypertension. *J Hypertens*. 2010;28:622–627.
9. Verberk WJ, Kroon AA, Kessels AGH, Dirksen C, Nelemans PJ, Lenders JWM, Thien TA, van Montfrans GA, Smit AJ, de Leeuw PW. Home Versus Office Blood Pressure Measurements: Reduction of Unnecessary Treatment Study: rationale and study design of the HOMERUS Trial. *Blood Press*. 2003;12:326–333.
10. Verberk WJ, Kroon AA, Lenders JW, Kessels AG, van Montfrans GA, Smit AJ, van der Kuy PH, Nelemans PJ, Rennenberg RJ, Grobbee DE, Beltman FW, Joore MA, Brunenberg DE, Dirksen C, Thien T, de Leeuw PW. Self-measurement of blood pressure at home reduces the need for antihypertensive drugs: a randomized, controlled trial. *Hypertension*. 2007;50:1019–1025.
11. Urquhart J, De Klerk E. Contending paradigms for the interpretation of data on patient compliance with therapeutic drug regimens. *Stat Med*. 1998;17:251–267, discussion 387–389.
12. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Refill persistence with chronic medication assessed from a pharmacy database was influenced by method of calculation. *J Clin Epidemiol*. 2006;59:11–17.
13. Vink NM, Klungel OH, Stolk RP, Denig P. Comparison of various measures for assessing medication refill adherence using prescription data. *Pharmacoepidemiol Drug Saf*. 2009;18:159–165.
14. Mar J, Rodriguez-Artalejo F. Which is more important for the efficiency of hypertension treatment: hypertension stage, type of drug or therapeutic compliance? *J Hypertens*. 2001;19:149–155.
15. Urquhart J. Partial compliance in cardiovascular disease: risk implications. *Br J Clin Pract*. 1994;73(suppl):2–12.
16. O'Rourke JE, Richardson WS. Evidence based management of hypertension: what to do when blood pressure is difficult to control. *BMJ*. 2001;322:1229–1232.
17. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther*. 1999;21:1074–1090.
18. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol*. 1997;50:105–116.
19. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf*. 2006;15:565–574.
20. Choo PW, Rand CS, Inui TS, Lee ML, Cain E, Cordeiro-Breault M, Canning C, Platt R. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. *Med Care*. 1999;37:846–857.
21. Burnier M, Schneider MP, Chioloro A, Stubi CL, Brunner HR. Electronic compliance monitoring in resistant hypertension: the basis for rational therapeutic decisions. *J Hypertens*. 2001;19:335–341.
22. Bertholet N, Favrat B, Fallab-Stubi CL, Brunner HR, Burnier M. Why objective monitoring of compliance is important in the management of hypertension. *J Clin Hypertens (Greenwich)*. 2000;2:258–262.
23. Waeber B, Vetter W, Darioli R, Keller U, Brunner HR. Improved blood pressure control by monitoring compliance with antihypertensive therapy. *Int J Clin Pract*. 1999;53:37–38.
24. Wetzels GE, Nelemans PJ, Schouten JS, Dirksen CD, van der Weijden T, Stoffers HE, Janknegt R, de Leeuw PW, Prins MH. Electronic monitoring of adherence as a tool to improve blood pressure control: a randomized controlled trial. *Am J Hypertens*. 2007;20:119–125.
25. Santschi V, Rodondi N, Bugnon O, Burnier M. Impact of electronic monitoring of drug adherence on blood pressure control in primary care: a cluster 12-month randomized controlled study. *Eur J Int Med*. 2008;19:427–434.