

Effects of Daily Adherence to Anti-Hypertensive Medication on Time-Varying Blood Pressure Control

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## ABSTRACT

Previous studies have shown that better adherence to anti-hypertensive medications is associated with improved blood pressure (BP) control over several months. Although most antihypertensive medications have a half-life of two days or less, little is known about the impact of poor adherence on BP control over a 7-day period. We examined this issue on a dataset of patients who monitored adherence using the Medication Events Monitoring System (MEMS caps) and had BP measurements in the course of routine clinical practice. We compared BP readings following seven days of excellent adherence (100%) or poor adherence (<60%), omitting BP values following intermediate adherence. In our first analysis, we examined 357 BP readings for 178 patients, controlling for patient-level covariates, and the half-life of the longest-lasting medication in the regimen. Our second analysis was limited to 14 patients who each recorded at least one period of poor adherence and one period of excellent adherence. In the first analysis, BP was 12/8 mm/Hg lower following a period of excellent adherence compared to poor adherence ( $p < 0.001$  for both SBP and DBP). In the second analysis, BP was 15/7 mm/Hg lower following a period of excellent adherence ( $p < 0.05$  for both SBP and DBP). We used extremely detailed adherence data and multiple analytic methods to estimate the impact of a 7-day period of poor adherence upon BP control compared to excellent adherence. This estimate can be useful for gauging the likely impact of poor adherence on BP in clinical medicine and randomized trials.

## BACKGROUND

Adherence is a well-known determinant of treatment response for numerous clinical conditions.<sup>1-2</sup> Over the past 40 years, a vast literature has centered upon understanding the effects of adherence, the determinants of adherence, and how best to improve adherence as a way to improve outcomes.<sup>3</sup> In the past, adherence was generally measured by patient self-report,<sup>4</sup> by pill counts, or using automated pharmacy records to assess gaps between fills.<sup>5</sup> Recent advances in the measurement of adherence include another tool: the Medication Event Monitoring System, or MEMS caps (Aardex, Switzerland). A MEMS cap records each bottle opening, allowing clinicians and researchers access to extremely detailed data regarding persistence with therapy and timeliness of dosing.<sup>6-8</sup>

While many studies have categorized patients into “adherent” and “nonadherent”,<sup>4</sup> most real patients have periods of better and worse adherence. Clinicians are commonly informed by a patient that his or her adherence has been less than perfect over the past week; it is unclear how they should use this information, because there are few available estimates of the expected impact on BP. It would therefore be useful to estimate the impact of poor adherence over a short period on the blood pressure (BP). There are at least three kinds of previous studies that might shed some light on the impact of a brief period of poor adherence on BP control, but each has shortcomings. Most medications, particularly at the time they are being considered for approval, are evaluated compared to placebo. This provides some information about the effect of a single medication under controlled circumstances. However, the

applicability to clinical practice is limited, because real-life regimens usually contain more than one drug, and real-life nonadherence is usually partial rather than complete.<sup>2, 8</sup> There are a few studies in which patients are instructed to stop their antihypertensive medications abruptly in order to compare the rebound effects of different medication classes over 7 days.<sup>9</sup> While such a study can provide valuable physiologic data, it also simplifies regimens down to one drug only and does not mirror real-world patterns of nonadherence. Finally, there are large retrospective database studies in which adherence is usually characterized using pharmacy fill data<sup>10-11</sup> or patient self-report.<sup>4-5</sup> Such studies have often shown that so-called “non-adherent” patients have worse BP control than “adherent” patients. Shortcomings of such a design include the unspecified time relationship between adherence behavior and BP measurements, as well as the oversimplification inherent in dividing patients using a binary adherence measure (adherent vs. nonadherent).<sup>2, 8</sup>

The availability of detailed adherence data from MEMS caps provides an opportunity to better characterize the effect on BP of a brief period of poor adherence in a real-world setting. We therefore examined data from a study on hypertension in which patients used MEMS caps to monitor adherence. We sought to characterize the precise relationship between a 7-day period of poor adherence to antihypertensive therapy and the resultant BP control.

## METHODS

### Data

The data for our analyses were obtained from the pre-intervention period of a randomized trial examining the effects of a provider-patient communication skill building intervention on adherence to anti-hypertension medication therapy and BP control (clinicaltrials.gov identifier: NCT00201149). Patients were enrolled from seven outpatient primary care clinics at Boston Medical Center, an inner-city safety net hospital affiliated with the Boston University School of Medicine. The study was approved by the Institutional Review Board of Boston University Medical Center.

Patients were recruited from August 2004 through June 2006 if they were of white or black race, at least 21 years old, and had an outpatient diagnosis of hypertension on at least three separate occasions prior to enrollment. Based on initial screening, patients were ineligible for the study if they already used a medication dispenser (as this might invalidate adherence data collection), were cognitively impaired, were of an ethnicity/race other than white or black, were unable to speak English, were not prescribed anti-hypertensive medication, were already participating in another hypertension study, or refused to participate.

Among 869 patients enrolled in the study who received dispensers with MEMS caps to monitor adherence to anti-hypertensive medication, 689 returned them. Our current study focuses on the medication-taking behavior of these 689 patients during the 90 days after the first opening of the MEMS cap. Rather than giving a patient multiple MEMS caps for all agents in their hypertension regimen, we gave one MEMS cap to each patient to correspond to one of their antihypertensive medications, asking them to use the MEMS cap for the most frequently taken medication. We characterized the medication-taking behavior of each patient using only this one medication, the

“index medication”. A similar strategy has been pursued in prior studies utilizing MEMS caps to characterize adherence to a multidrug regimen which have found that adherence to an index medication generally correlates with adherence to the entire regimen.<sup>8, 14-16</sup>

We imposed additional restrictions to increase the homogeneity of the sample. Over the first 90 days after issuance of the MEMS cap, a patient needed at least two clinic visits with BP readings to be part of our final sample. Ensuring multiple BP readings per patient reduced the potential for confounding effects of adherence and characteristics specific to a patient. We excluded one patient whose index medication changed during the first 90 days, and excluded three others whose dose frequency for the index medication changed from twice to once daily during the first 90 days. Furthermore, if a patient opened his/her MEMS cap more than twice per day over 10% or more of the monitored period, then the patient was excluded because of suspicion that the patient did not understand the MEMS cap and was not using it correctly. This resulted in a final study sample of 200 patients, all of whom were taking the index medication once per day.

### **Independent Variable: Adherence to Therapy**

We characterized adherence to antihypertensive therapy using MEMS caps . These devices use a microchip to record all bottle openings. Adherence as measured by MEMS caps has been linked to improvements in numerous clinical outcomes,<sup>13, 17-18</sup> including hypertension control.<sup>14-15</sup> Clinicians were not given feedback about their patients' adherence as measured by MEMS caps.

The MEMS cap data for this sample were cleaned in the following manner. For non-monitored periods (e.g., hospitalizations), the number of MEMS cap openings were set to “missing.” A patient was considered adherent on days in which the MEMS cap was recorded to have been opened exactly once or twice, and was considered non-adherent if the MEMS cap was not opened. On days where the MEMS cap was opened more than twice, the number of openings was set to “missing” due to the extra uncertainty in the reason for the multiple openings.

### **Dependent Variable: Clinical Blood Pressure Measurements**

Blood pressure was taken for each patient at irregular intervals, as part of routine clinical care. Blood pressures could be taken using manual or electronic devices, by clinical staff including physicians, nurses, and medical assistants, and were recorded in the electronic medical record. If multiple readings were taken on a single day, the values were averaged for our study. We separately examined systolic and diastolic blood pressures (SBP and DBP) as outcomes.

### **Control variables**

We recorded gender, self-reported race (white versus black) and age at study inception. Using both ICD-9 codes and problem lists from the electronic medical record, we noted whether the patients had the following comorbid conditions, all of which could impact the blood pressure, the use of antihypertensive medications, or the perceived urgency of controlling hypertension: benign prostatic hypertrophy, cerebrovascular disease, congestive heart failure, chronic kidney disease, coronary artery disease,

diabetes mellitus, hyperlipidemia, obesity (BMI > 30), peripheral vascular disease, and tobacco use.

We also categorized the degree of “forgiveness” of the patient’s overall antihypertensive regimen. Urquhart coined the term “forgiveness” to describe the degree to which a medication continues to work well even when an occasional dose is omitted.<sup>19</sup> We hypothesized that the impact of poor adherence might be blunted if the patient is using a regimen with higher forgiveness. Each patient was placed into one of three groups, based upon the most “forgiving” medication in the regimen: patients receiving only medications with short-term biologic effects, primarily beta blockers or any drug ordinarily given twice a day or more (“low forgiveness”); patients whose regimen included a thiazide diuretic, which has long-lasting effects and is particularly resistant to brief lapses in adherence (“high forgiveness”);<sup>9</sup> and all other regimens (“intermediate forgiveness”). One of the authors (AJR) manually examined the entire antihypertensive regimen (not just the index medication) to assign these categorizations.

### **Patient Adherence Example**

An example of the relationship between MEMS cap openings and BP measurements can be seen for one of the patients in our study (Figure 1). The horizontal axis counts the number of days since the patient entered the study, and the vertical axis counts the number of MEMS cap openings on each day displayed as black dots. For this patient, three clinic visits occurred in which BP readings were taken, with the days represented by the vertical lines, and the DBP and SBP indicated by diamonds

on the lines. The seven days preceding the BP visits are shaded. In the seven-day period preceding the first visit, the patient had excellent adherence (one pill per day), and the BP reading was 110/70. For the subsequent two visits, the adherence was at 0% for the seven-day period preceding the BP readings, and the corresponding BP measurements were 130/84 on the first visit, and 145/92 on the second visit. This example provides an informal basis for the statistical analyses we apply to these data.

### **Statistical Analysis**

Two distinct approaches were taken to assess the effects of adherence upon BP. The first approach treated each blood pressure reading as a separate outcome, and used adherence over the preceding 7 days to predict blood pressure. The second approach restricted the sample to patients who had two or more blood pressure readings, one of which was preceded by excellent adherence and one of which was preceded by poor adherence. Thus, using the first approach, we analyzed a large fraction of our study sample with the intention of adjusting for between-patient differences through the control and health factors. In the second approach, every patient served as his/her own control and it was not necessary to control for covariates. In both cases, recent adherence prior to a blood pressure reading was determined based on the percentage of days in which the patient opened the MEMS cap. Adherence was considered “poor” if adherence was less than 60%, and was “excellent” if adherence was 100%. Blood pressure readings preceded by a 7-day period with “intermediate” adherence (between 60% and 100%) were removed from this analysis. All models were separately fit to predict SBP and DBP.

In our first analytic approach, adherence was computed for the 7 days prior to each blood pressure reading. Blood pressure readings were excluded if they occurred within the first 7 days of a patient's entry to the study. Random effects least-squares regressions were fit to the resulting data; blood pressure (SBP and DBP) were regressed on an excellent/poor adherence indicator, along with gender, race, age (in years, categorized into 0-59, 60-69, 70-79, and 80+), comorbid conditions, and the forgiveness of the regimen, with a normally distributed mean-zero random effect per unique patient. In this way, we compared blood pressures following periods of excellent vs. poor adherence, while controlling for measured patient characteristics and patient identity as a random effect.

Our second approach limited the analyses to patients who had at least one period each of poor and excellent adherence within the 90 day study window. The analyses consisted of random effects least-squares regressions in which SBP and DBP were regressed on binary indicators of “excellent” versus “poor” adherence 7 days prior to the reading, with normally distributed mean-zero patient-specific random effects. The random effects models were fit using the “lme” function in the statistics software package R.<sup>20</sup>

## RESULTS

For Analysis 1, we studied only BP readings preceded by a 7-day period of poor (<60%) or excellent (100%) adherence, eliminating BP values preceded by a period of intermediate adherence. As shown in Table 1, the sample for Analysis 1 consisted of

178 patients: 29% were male, 41% were of white race, and ages ranged from 25 years to 86 years with a mean age of 60.5 (SD = 10.7). The Analysis 1 group had a considerable burden of comorbidity (for example, 40% had diabetes). About 60% of patients were taking a high-forgiveness regimen (one that included thiazide diuretics), while 6% were taking a low-forgiveness regimen and the remaining 34% were taking an intermediate-forgiveness regimen.

Analysis 1 included a total of 357 blood pressure readings for 178 unique patients. For 7-day periods with poor adherence, the average adherence rate was 34% with a standard deviation of 22%. Table 2 summarizes the main results for Analysis 1. Without controlling for forgiveness of the regimen, but controlling for demographics and comorbid conditions, BP readings following periods of excellent adherence were lower than those following periods of poor adherence (SBP -11.6 mm/Hg, DBP -7.7 mm/Hg,  $p < 0.001$  for both). We then added an interaction term between adherence and the forgiveness of the regimen; this interaction term did not significantly improve the model fit, though adherence in the SBP model was only significant at the 0.01 level. Based on the trends of the coefficient estimates, the effect of adherence upon SBP was more pronounced when the patient was taking a low-forgiveness regimen, although this effect was not statistically significant.

In Analysis 2, 14 patients had at least one BP value preceded by a period of poor adherence (<60%) and at least one BP value preceded by a period of excellent adherence (100%). These 14 patients contributed a total of 36 observations. During the 90-day study window, 8 of the patients had excellent adherence always followed by poor adherence, 5 had poor adherence always followed by excellent adherence, and

one patient had both poor and excellent adherence following each other. For 7-day periods with poor adherence, the average adherence rate was 33% with a standard deviation of 24%, nearly identical to the results from Analysis 1. The Analysis 2 group appeared to have a higher burden of comorbidity than the Analysis 1 group, although between-group differences were not statistically significant. Accounting for patient random effects, mean BP following excellent adherence was 130.6/78.1, compared to 145.5/85.2 following poor adherence, a difference of 15.0/7.1 mm/Hg ( $p < 0.05$  both for SBP and DBP).

In both analyses, we examined alternative window periods prior to BP readings (vs. the base case definition of 7 days), and different definitions of “excellent” and “poor” adherence (vs. the base case definitions of 100% and <60%). In general, the results were similar, although extending the window length excluded a larger number of patients, and decreasing the window length resulted in somewhat less powerful effects of adherence on BP. Increasing the percent threshold for poor adherence (e.g., to 80%) attenuated the effect of poor adherence on BP.

## DISCUSSION

In this study, we estimated the effect size of adherence on BP control. By focusing on 7-day periods characterized by excellent (100%) or poor (<60%) adherence, we were able to show that the difference between these two is approximately 12/8 or 15/7 mm/Hg, in our first and second analyses respectively. Our second analysis, although limited to only 14 patients, allowed each patient to serve as

his or her own control. The effect size we found is robust to the method of analysis; it was similar whether we included a large number of patients and controlled for several potential confounding factors, or whether we only included patients for whom both poor and excellent adherence periods were observed. This paper, therefore, provides a methodologically robust estimate regarding the impact of poor adherence upon BP control over a 7-day period.

Previous efforts to estimate the effect size of nonadherence upon BP have been limited by assessing both adherence and BP control in less-than-optimal ways (binary measures of control, binary measures of adherence, unclear timing between the two). In a seminal study, Morisky et al. developed a 4-item scale to measure self-reported nonadherence and then demonstrated the criterion validity of this measure.<sup>4</sup> In that study, 75% of patients deemed adherent by the scale had controlled BP at 5 year follow up, compared to 47% of patients deemed nonadherent by the scale. In another well-known study, the authors used automated pharmacy fills data to assess adherence and again found that non-adherence over a 30-day period was a risk factor for uncontrolled BP.<sup>10</sup> In contrast, our study quantifies the effect size of adherence in terms of mm/Hg rather than limited to a binary outcome of controlled/uncontrolled, and does so over a 7-day period. Previous studies have shown that it may not be sufficient to characterize patients as “adherent” or “nonadherent”, because patients may have periods of excellent adherence interspersed with “drug holidays”, or periods during which the medication is intentionally omitted for several days.<sup>7-8, 19, 21-22</sup> Because long-term adherence is not a binary concept, it is important to understand the impact of short-term

adherence on the outcome of interest rather than simply labeling some patients as “nonadherent” and then demonstrating that they have inferior BP control.

Our findings have utility for clinicians who treat hypertension. Patients often arrive at a visit not having taken their medication for one or more days, and this can serve in some cases as an excuse for the clinician to label them “nonadherent”, to ascribe their poorly controlled BP to this nonadherence, and in many cases to omit possibly beneficial intensification of the antihypertensive regimen.<sup>23-24</sup> These results also remind us of the complexity of adherence and the variations – even within specific patients – in adherence patterns over time, and the potential oversimplification of labeling patients as completely adherent or completely nonadherent. The results of this study suggest that a considerable degree of non-adherence over the 7-day period prior to a BP measurement may account for an increase in the BP by about 12-15/7 mm/Hg. This estimate can help clinicians correlate their clinical observations of BP readings with the reported extent of recent nonadherence. In addition, our findings have relevance to researchers who study hypertension, particularly in the setting of clinical trials.

While the results of our study are compelling, we do acknowledge some important limitations. First, and most importantly, we cannot establish causal effects of non-adherence from our observational data. Second, we used a carefully selected subset of patients who recorded periods of excellent or poor adherence, and for the second analysis, patients who recorded at least one of each. Not only did this sample selection necessarily limit our sample size, but it arguably could impact generalizability. By limiting our study to patients that had multiple BP measurements in 90 days, we may have selected for a sicker group of patients. In addition, the second analysis was

restricted to patients who had periods of both excellent and poor adherence, so that by design this particular sample had more erratic behavior than the general hypertensive population. However, because the estimated effect sizes from the two analyses were consistent, this concern may not be a serious one. Further, the consistent results between the two analyses greatly enhanced validity because using each patient as his or her own control is arguably the gold standard for controlling for confounding due to patient-specific factors. A third limitation is that we tracked adherence using the index medication, i.e. the medication whose bottle had a MEMS cap. However, most of these patients were taking other medications as well, which were not monitored by MEMS caps. This is a usual practice in adherence research,<sup>8, 15</sup> and previous studies have shown that adherence to an index medication matches well with adherence to other medications in the regimen. Furthermore, there is no accepted method available for harmonizing the results of multiple simultaneous MEMS caps. Finally, our study enrolled patients from a single medical center, an inner-city safety net hospital with a high proportion of minority and immigrant patients. This also may impact generalizability.

In summary, this study provides a fairly precise estimate of the effect of adherence on BP control in the short term: 7 days of poor adherence (<60%) increases BP by approximately 12-15/7 mm/Hg compared to 7 days of excellent adherence. This finding will have great utility for clinicians and researchers who study hypertension.

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Table 1: Sample characteristics

	Analysis 1 (178 Patients)	Analysis 2 (14 Patients)
Male	29%	36%
White	41%	43%
Nicotine dependence	7%	7%
Hyperlipidemia	56%	43%
Diabetes	40%	50%
Peripheral vascular disease	7%	21%
Renal insufficiency	6%	7%
Benign prostatic hypertrophy	4%	7%
Coronary artery disease	19%	36%
Congestive heart failure	6%	14%
Cerebral vascular disease	5%	7%
Obese	60%	57%
<u>Forgiveness of regimen</u>		
Low Forgiveness	6%	7%
Intermediate Forgiveness	35%	29%
High Forgiveness	60%	64%
Age in years [mean (sd)]	60.5 (10.7)	61.9 (12.3)

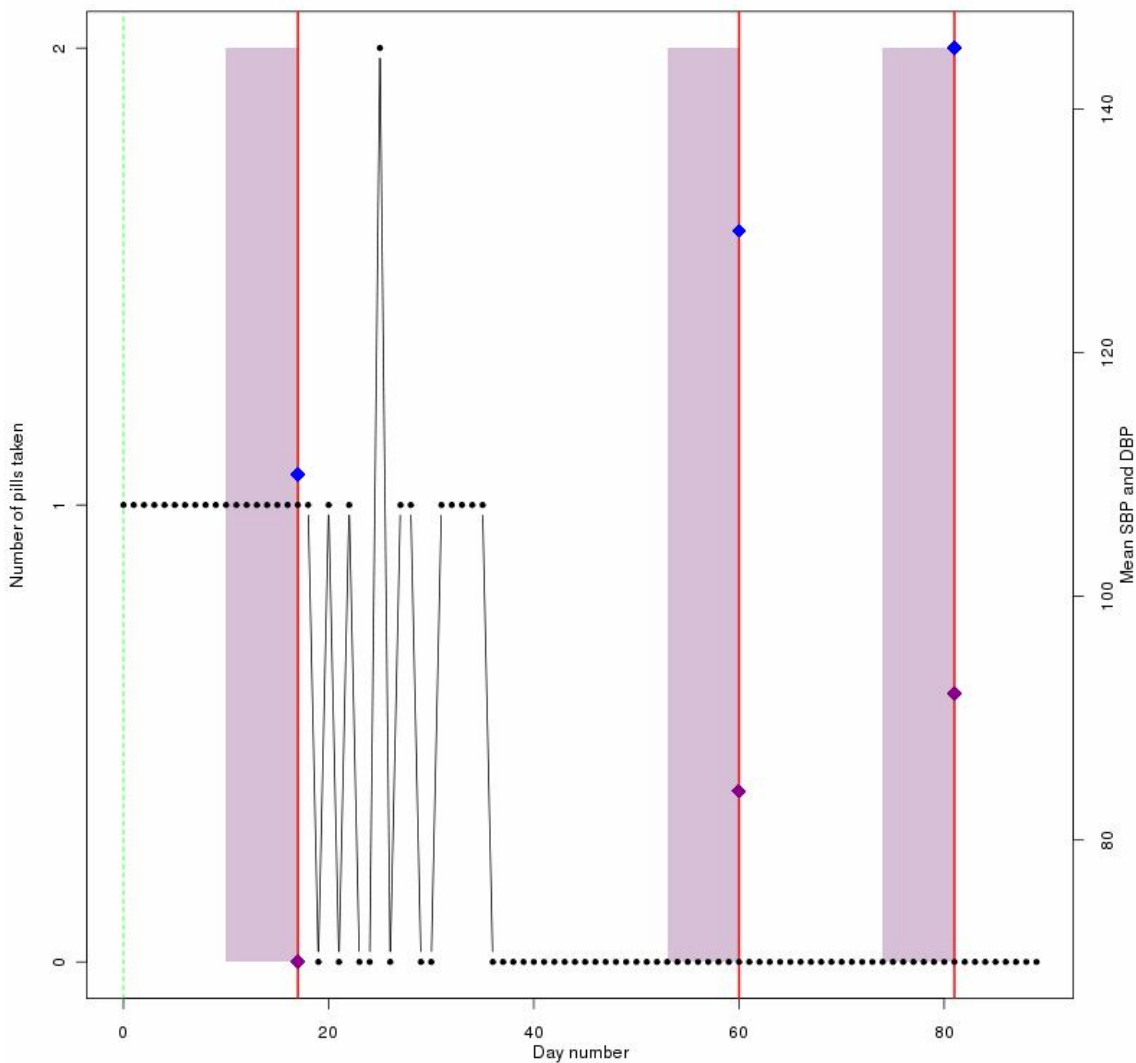
No significant differences at the 0.05 level were found between the 14 patients in Analysis 2 and the 164 (distinct) patients in Analysis 1 for any of the patient characteristics.

Table 2: Models for effect of excellent versus poor adherence based on full sample

	Systolic BP		Diastolic BP	
	w/o Medication Forgiveness	with Medication Forgiveness	w/o Medication Forgiveness	with Medication Forgiveness
Intercept	137.72 (3.79)	136.68 (4.27)	89.71 (2.18)	90.48 (2.44)
Adherent	-11.62 (2.80) ***	-11.21 (3.44) **	-7.70 (1.61) ***	-8.90 (1.97) ***
Male	2.49 (2.76)	2.84 (2.79)	2.26 (1.59)	2.41 (1.59)
White	-2.73 (2.42)	-2.02 (2.45)	-2.04 (1.39)	-1.88 (1.40)
Age Group				
Age < 60	REF	REF	REF	REF
Age 60-69	2.92 (2.69)	3.77 (2.75)	-3.27 (1.55) *	-2.91 (1.57)
Age 70-79	6.42 (3.38)	7.79 (3.46) *	-4.70 (1.94) *	-4.26 (1.97) *
Age 80+	13.56 (6.86) *	13.40 (6.95)	-9.62 (3.95) *	-9.10 (3.96) *
Nicotine dependence	-0.79 (4.32)	-0.77 (4.35)	2.37 (2.49)	2.26 (2.48)
Hyperlipidemia	1.43 (2.41)	1.78 (2.43)	-2.17 (1.39)	-2.10 (1.39)
Diabetes	-2.74 (2.64)	-2.88 (2.66)	-4.30 (1.52) **	-4.40 (1.51) **
Peripheral vascular disease	-6.74 (4.75)	-7.44 (4.78)	-4.38 (2.73)	-4.86 (2.73)
Renal insufficiency	0.24 (5.16)	0.032 (5.19)	1.48 (2.97)	1.34 (2.96)
Benign prostatic hypertrophy	-0.99 (6.41)	-1.14 (6.48)	-3.03 (3.69)	-2.96 (3.69)
Coronary artery disease	1.09 (3.28)	1.32 (3.31)	-2.09 (1.89)	-2.13 (1.89)
Congestive heart failure	2.75 (5.24)	4.10 (5.38)	2.55 (3.02)	2.79 (3.06)
Cerebral vascular disease	13.67 (5.89) *	13.34 (5.96) *	0.26 (3.39)	0.27 (3.40)
Obese	2.28 (2.51)	2.19 (2.54)	1.50 (1.45)	1.48 (1.45)
Forgiveness of Medical Regimen				
Low Forgiveness	--	-21.07 (16.68)	--	-17.39 (9.61)
Intermediate Forgiveness	---	2.36 (5.70)	---	-1.83 (3.27)
High Forgiveness	---	REF	---	REF
Adherent x Low Forgiveness	---	27.52 (16.87)	---	20.56 (9.73) *
Adherent x Intermediate Forgiveness	---	-4.78 (6.19)	---	1.65 (3.55)

Table entries are coefficient estimates (standard errors). \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ .

Figure 1: Example patient profile



The number of pills taken on each day of the study for a selected patient. The three vertical lines indicate clinic visit days on which BP readings were taken, and the diamonds on each line denote the SBP and DBP at the visit (labeled on the right). The shaded rectangular areas mark off seven days prior to each clinic visit.