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# Intensifying Therapy for Hypertension despite Suboptimal Adherence

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## Abstract

More intensive management can improve control blood pressure (BP) in hypertensive patients. However, many would posit that treatment intensification (TI) is not beneficial in the face of suboptimal adherence. We investigated whether the effect of TI upon BP varies by adherence. We enrolled 819 patients with hypertension, managed in primary care at an academically-affiliated inner-city hospital. We used the following formula to characterize TI: (visits with a medication change - visits with elevated BP)/total visits. Adherence was characterized using electronic monitoring devices ("MEMS caps"). Patients who returned their MEMS caps (671) were divided into quartiles of adherence, while patients who did not return their MEMS caps (148) had "missing" adherence. We examined the relationship between TI and the final systolic blood pressure (SBP), controlling for patient-level covariates. In the entire sample, each additional therapy increase per 10 visits predicted a 2.0 mm/Hg decrease in final SBP ($p < 0.001$). After stratifying by adherence, in the "best" adherence quartile each therapy increase predicted a 2.1 mm/Hg decrease in final SBP, followed by 1.8 for the "next-best" adherence quartile, 2.3 in the third quartile, and 2.4 in the "worst" adherence quartile. The effect size for patients with "missing" adherence was 1.6 mm/Hg. The differences between the group with "best" adherence and the other 4 groups were not statistically significant. In this observational study, treatment intensification was associated with similar BP improvement regardless of the patient's level of adherence. A randomized trial could further examine optimal management of patients with suboptimal adherence.

### Keywords

Hypertension; adherence; medication therapy management; quality of care; ambulatory care

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## INTRODUCTION

For almost 30 years, we have known that more intensive management of hypertension can improve blood pressure (BP) control, both in the setting of clinical trials[1] and in observational studies of routine clinical practice.[2, 3] Similarly, it has long been appreciated that greater adherence to medication regimens can improve BP control.[4, 5] More recently, there have been several efforts to understand the relationship between adherence and treatment intensity (TI) in the management of hypertension.[6–10] Some of these studies have addressed whether clinicians are more or less likely to increase therapy according to patient adherence,[6, 7] while others have probed the relationship between TI and adherence in determining BP control over time.[8–10]

Explorations of the relationship between TI and adherence in determining BP control have been limited in their scope, mostly demonstrating that both TI and adherence have important effects on BP control.[8–10] However, a more important question has not yet been addressed, namely whether the effect of TI upon BP control differs by adherence. This information would help inform the difficult clinical decision of how best to manage a patient suspected of suboptimal adherence to therapy. Despite the lack of evidence regarding this topic, there seems to be widespread agreement that it is not advisable to intensify therapy when a patient is nonadherent.[7, 8, 11] This may be due to a belief, on the part of clinicians, that nonadherent patients may not benefit from treatment intensification, and that it in fact may harm them by predisposing to hypotensive episodes when therapy is actually taken. However, the conviction that therapy should not be increased for nonadherent patients has not been subjected to empirical evaluation, and it seems to be based on a binary view of patients as completely adherent or completely nonadherent, when in fact most patients fall somewhere in between.[12]

We therefore set out to examine the association between TI, adherence, and BP control. Our study had two objectives: 1) to determine whether patient adherence to antihypertensive therapy predicts clinician decisions regarding therapy intensification and 2) to determine whether the effect of TI on BP control differs among strata of adherence. We hypothesized that patients with suboptimal adherence would indeed have improved BP control with more intensive therapy, because a more potent regimen, even one taken less than 100% of the time, is likely to be more effective in controlling BP.

## METHODS

### Enrollment

This report is a secondary analysis of data from a randomized trial designed to test whether a clinician-directed curriculum about patient-centered counseling could improve doctor-patient communication, adherence to therapy, and blood pressure 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. We identified all patients of White or Black race, age 21 and older, with outpatient diagnoses of hypertension on at least three separate occasions between August 2004 and June 2006. Because of this requirement for three previous outpatient diagnostic codes, our study enrolled only patients with prevalent as opposed to incident hypertension. Study staff then tracked the clinic visits of these 10,125 patients over a 19 month period, and, as they presented for care, approached 3526 of them to request participation in the study. Of those, 654 patients (19% of 3526) overtly refused to participate and 920 patients (26% of 3526) responded that they did not have time to participate, but we were unable to assess their eligibility before they declined. All willing respondents were then asked a series of questions and administered a cognitive screen to determine eligibility; 1083 patients (55% of the remaining

1952) were excluded, for reasons detailed in Figure S1 (please see http://hyper.ahajournals.org). Assuming a similar rate of ineligibility among patients whose eligibility was not assessed, we recruited 869 patients from a likely pool of 1578 eligible patients (55%).

### Dependent Variable: Final Systolic Blood Pressure

The primary outcome was each patient's final SBP value, i.e. the one immediately prior to study completion. These BP values were drawn from the clinical record of Boston Medical Center. We chose SBP rather than diastolic blood pressure as our primary outcome, because many more patients have poorly-controlled SBP.[13, 14]

### Categorizing Medication Increases

Automated data from Boston Medical Center's electronic medical record (EMR) were examined. Our database included all prescriptions written, as well as all clinical BP values recorded within the study period. The unit of analysis was a visit to the primary care clinic, as identified by a date on which a BP value was recorded. When there were multiple BP values recorded on one date, we chose the one with the lowest SBP; if two values were tied, we selected the one with the lower DBP.

We recorded the patient's initial regimen of antihypertensive medications, i.e. the regimen prior to study inception. One of the authors (AJR) manually reviewed all prescriptions for each patient to see when the BP regimen was increased. An increase in medication was defined as either a new medication being added to the regimen or an increase in the dose of an existing medication. The period between each two BP values was assigned a 1 if the regimen was increased during that period, or a 0 if it was not. Multiple increases during a single period were counted as a 1. A subset of 42 patients, representing 495 (5%) of all clinic visits, were randomly selected for blind re-abstraction by another author (DRB). Agreement between the two reviewers was excellent (kappa = 0.93, 95% CI 0.87–0.98).

### Independent Variable: Treatment Intensity Score

We characterized TI using an observed-expected scoring system originally described by Okonofua, et al.[3] We have shown that this scoring system is a valid predictor of BP control over time, and is the preferred scoring system to measure TI in the care of hypertension.[15] One of the strengths of this measure is that it avoids confounding by severity, the tendency for patients with more severe disease to receive more intensive management.[15] Without accounting for confounding by severity, one can obtain the paradoxical result that more intensive management is associated with worse control of BP.[15] Because this TI measure inherently accounts for BP control, it is not necessary to also control for initial BP as a covariate.

For this TI measure, a medication increase is expected on each occasion when the recorded BP is 140/90 mm/Hg or higher. Using this number, and the number of occasions on which the regimen was intensified, each patient was assigned a score between −1 and 1, using the following formula:

$$(\text{observed medication changes} - \text{expected medication changes})/\text{number of clinic visits}$$

As an example, over a period of 10 visits, 5 of which had an elevated BP value, a patient would have an expected proportion of visits with medication increases of 5/10. If this patient actually had 3 visits with medication increases, the score would be 3/10 − 5/10 = −0.2, indicating that therapy was increased at 20% fewer visits than expected. If the patient had 6 visits with therapy

increases, the score would be 6/10 − 5/10 = 0.1, indicating that therapy was increased at 10% more visits than expected.

We recognize that for patients with diabetes or chronic kidney disease, current guidelines set a lower BP target (i.e. 130/80 mm/Hg).[13] We therefore created an additional TI score only for patients with a low BP target. For this alternative TI score, a medication increase was expected on each occasion when the recorded BP is 130/80 mm/Hg or higher, as opposed to 140/90 mm/Hg for the main TI score. We conducted a sensitivity analysis, dividing the sample into patients with the higher and the lower BP thresholds, and repeating our analyses for each group separately using the appropriate TI score. Results were similar to our main analysis, and are not shown.

### Stratification Variable: Adherence to Antihypertensive Therapy

We characterized adherence to antihypertensive therapy using Medication Events Monitoring System ([MEMS], AARDEX, Zurich, Switzerland). 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,[16, 17] including hypertension control.[18, 19] Patients were each given one MEMS cap, corresponding to the antihypertensive medication that they took the most times per day. Clinicians were not given feedback about their patients' adherence as measured by MEMS caps.

When processing MEMS data into adherence scores, we began by identifying all patients who either did not return their MEMS cap or did not open it enough times to calculate an adherence score (for example, once). For all others, we used MEMS data from the first 90 days after they began using their MEMS cap, or a shorter period for patients who stopped using their MEMS cap sooner. We calculated the proportion of days in this period on which the patient took at least the number of doses prescribed. Patients who did not return their MEMS caps were considered to have "missing" adherence. The remaining patients were divided into quartiles by adherence; thus, there were five adherence groups included in the analysis: four quartiles and "missing".

### Covariates

We collected patient demographic data, including self-reported race (Black or White), gender, and age. Using both ICD-9 codes and problem lists from the EMR, 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, chronic heart failure, chronic kidney disease, coronary artery disease, diabetes mellitus, hyperlipidemia, obesity (BMI > 30), and peripheral vascular disease. We noted whether patients were actively using tobacco at any time during the study.

Finally, we controlled for assignment to the intervention or control arm of the parent randomized trial as a covariate. Clinicians treating the patients in the study arm received a one-time educational intervention designed to improve doctor-patient communication and cultural competency; clinicians treating patients in the control arm did not receive the intervention.

### Statistical Analyses

We compared baseline characteristics among the five adherence groups, using ANOVA and chi-square tests as appropriate. We used a test of linear trend to compare TI scores among the five adherence strata. We examined the effect of TI on the final SBP using a generalized linear model, controlling for patient-level covariates. We then added interaction terms to our model to test whether the effect of TI on the final SBP differed among the adherence strata, controlling

for patient-level covariates. Finally, we analyzed each adherence stratum separately, controlling for covariates, to confirm that the effect of TI upon SBP remained statistically significant in all strata. For all analyses, we used SAS, version 9.1 (SAS Institute, Cary, NC).

## RESULTS

### Patient Characteristics

Of the 869 patients enrolled in the study, 50 were not analyzed because they had 2 or fewer BP values. Therefore, 819 patients with hypertension, all managed at Boston Medical Center, constituted our study population (Table 1). The mean follow-up time was 24 months; on average, patients visited the clinic once every two months. The mean age was 59.6 years, 34% of patients were male, and most (58%) were of Black race. Considering their relatively young age, the population had a relatively high burden of comorbidity: 33% had diabetes, 13% had coronary artery disease, 7% had chronic kidney disease, and 59% were obese. Most patients (74%) were receiving two or more antihypertensive medications at the beginning of the study. The population was characterized by relatively well-controlled hypertension at baseline: the mean initial BP was 134/80 mm/Hg, and 55% of patients had an initial BP below 140/90 mm/Hg.

There were five adherence groups: four quartiles of adherence (98% and higher, 94–98%, 80–94%, below 80%) and patients who did not return their MEMS caps (missing adherence). Within the poor adherence quartile, the median adherence was 62% (Interquartile Range 42%–73%). Comparison of baseline characteristics among these 5 adherence strata revealed several differences (Table S1, please see http://hyper.ahajournals.org). Most notably, Black race was associated with poorer adherence or not returning the MEMS cap; the best adherence group contained 45% Black patients, compared to the worst adherence group (69%) and the missing adherence group (76%, $p < 0.001$ for chi-square test). In addition, patients with poor or missing adherence had worse BP control at baseline. For example, 45% of patients with missing adherence and 50% of patients with the worst adherence had controlled BP at baseline, compared to 61% among patients with the best adherence (p value for chi-square test = 0.03).

### Treatment Intensity, Adherence, and Blood Pressure Control

Blood pressure was elevated at 4,894 of 11,530 clinic visits (42%), and therapy was increased at 7.4% of 11,530 visits. The median TI score was −0.25 (IQR −0.06, −0.50); the mean was −0.28 (SD 0.29). Among the 671 patients with complete adherence data, the average patient was adherent on 85% of days (median 94%, Interquartile Range 80%–98%). Patients with better adherence received more intensive management (Table 2). The difference in the mean TI between the best and worst adherence quartiles was 0.09, approximately equivalent to one extra therapy increase per 11 clinic visits.

In the entire sample of 819 patients, each additional therapy increase per 10 visits predicted a 2 mm/Hg decrease in the final SBP, after adjusting for covariates ($p < 0.001$). We added interaction terms (Table 3) to reflect membership in the other adherence groups, compared to the reference category (best adherence). The effect size in the best adherence group was a 2.1 mm/Hg decrease in SBP for each additional therapy increase per 10 visits. The effect sizes in the other adherence groups were 1.8 mm/Hg in the second quartile, 2.3 mm/Hg in the third quartile, 2.4 mm/Hg in the fourth (worst) adherence quartile, and 1.6 mm/Hg among patients with missing adherence. These effect sizes did not differ from that of the best adherence group at the 0.05 level of significance. In addition, we re-ran the multivariate regression separately for each adherence stratum; the effect of TI upon final SBP remained statistically significant for each stratum ($p = 0.01$ for missing adherence and $p < 0.001$ for all other groups).

We also explored the effect of TI for patients with even lower adherence to therapy than the worst adherence quartile: less than 60% adherence (n = 75). The effect of TI in that group, controlling for covariates, was similar to our other analyses (final SBP 2.0 mm/Hg lower for each additional therapy increase per 10 visits, p = 0.006).

## DISCUSSION

In this observational study, we investigated the interaction of adherence and TI in determining BP control. We found that more adherent patients received somewhat more intensive management, suggesting that clinicians may hesitate to intensify therapy in the face of suspected nonadherence. We also found that greater TI was associated with improved BP control over time, and that this effect was similar in size for patients with varying levels of adherence. This is a non-intuitive finding, and one which may surprise many. We would suggest that the key to understanding this finding is to remember that adherence is not a binary concept, with patients divided into those who are "adherent" and those who are "non-adherent". In our study, even patients with the worst adherence generally took approximately half their doses of medication. Many antihypertensive medications have long half-lives, and drugs with long half-lives may have a degree of "forgiveness" when some doses are missed.[20] Previous studies have shown that blood pressure response to many antihypertensives persists for several days after the last dose was taken, although the period of "forgiveness" varies among drugs.[21]

Many clinicians address suspected nonadherence by asking the patient to improve adherence, and then rechecking the BP at the next visit. This strategy may well reduce treatment intensity over time, especially if another reason not to intensify therapy is found at the following visit.[2, 3, 22] Our results suggest that, while clinicians in our study were less likely to intensify therapy in patients with suboptimal adherence, they could have improved these patients' BP control considerably by intensifying therapy. We do not mean to suggest that it is not worthwhile to address suboptimal adherence the evidence is quite clear that greater adherence improves BP control.[4, 5] However, it is notoriously difficult and effort-intensive to improve adherence, and not all patients will respond to such efforts.[23, 24] Indeed, we know that clinicians often are not even aware of issues with adherence.[25–27] While improving adherence remains an important priority, our results suggest that clinicians need not reserve therapy increases for patients with ideal adherence to therapy.

Our study population, in general, had a relatively high degree of adherence to therapy, which some might find surprising among an urban safety net population. It is important to note, however, that previous studies using MEMS caps to characterize adherence to antihypertensive medications have recorded similar degrees of adherence. For example, Choo et al. studied patients in a managed care organization in Massachusetts and found that the mean percentage of days with adherence was 86%, and the median was 92% (IQR 0.77–0.98).[28] By comparison, we found a mean adherence of 84% and a median of 94% (IQR 0.80–0.98). In another study, Fung et al. found that 27% of Medicare + Choice beneficiaries were poorly adherent, defined as taking less than 80% of their medication;[29] in our study, 24% of patients were less than 80% adherent. These comparisons remind us that divergent patient populations can have very similar patterns of adherence, and suggest that our results may be broadly generalizable to other populations.

Our study has several limitations. First, although MEMS caps have strengths as a measure of adherence,[26–28, 30–32] they also have weaknesses.[28, 33] Patients may take their medication more often than MEMS data would suggest, particularly if they are using some other sort of pill box rather than the bottle used for the MEMS cap.[33] We made efforts to minimize this effect, excluding patients from our study who stated that they use a pill organizer, but it is still possible that some patients identified as very poorly adherent in our study were actually quite

adherent to their medication, but not to using the MEMS cap. Similarly, we cannot fully characterize adherence among patients who did not return their MEMS caps. However, the fact that these patients had higher BP at baseline than those with complete MEMS data supports the contention that these patients may have had the worst adherence of all. In any event, patients with incomplete MEMS data also benefited from TI.

Second, this study did not examine definitive outcomes of care such as cardiovascular events or mortality. However, improved BP control (an intermediate outcome) has robustly been tied to improvements in morbidity and mortality.[13] In addition, it is possible that patients whose therapy was intensified despite non-adherence experienced some episodes of hypotension, a commonly raised concern in such a situation. This would raise concerns that, while more intensive management of hypertension in suboptimally adherent patients might lower BP, it might also increase risk for adverse events. However, there were no hypotensive episodes reported to study staff by patients or clinicians.

Third, this study shares the limitations of any observational study. While our results suggest that patients with less-than-ideal adherence do benefit from intensification of the antihypertensive regimen, it cannot determine the ideal management for a non-adherent patient with hypertension. A randomized trial could assign non-adherent patients to intensification, adherence interventions, both, or neither, and would be ideally suited to answer this question. Fourth, we had few, if any, patients in our study who took none of their medication at all. Our results may not apply to such uncommon patients, and we would agree that intensifying antihypertensive therapy for such a patient would not be beneficial. Fifth, our study enrolled only patients with prevalent as opposed to incident hypertension. Therefore, our findings may not be generalizable to patients with newly diagnosed hypertension, who may have different patterns of adherence. Sixth, this study relies upon data from one medical center, which may not be representative of other settings. Boston Medical Center is an academic, inner-city safety net hospital. Its academically oriented clinicians and largely immigrant and poor patient population are a somewhat unique combination. These results remain to be confirmed in other settings.

Finally, there are many legitimate reasons why a clinician-patient dyad might decide not to intensify therapy, including competing priorities, medication side effects, and patient unwillingness to accept a more intensive regimen. We do not mean to suggest that intensifying therapy is always the correct response to an elevated BP value. Rather, our study suggests that, when therapy intensification is mutually acceptable to the patient and the clinician, and there are no other reasons not to intensify, then suboptimal adherence alone is not a sufficient reason to forego intensification. While it is important to communicate effectively about adherence and to try to improve it, it is not necessary to await proof of perfect adherence before intensifying therapy for hypertension.

## PERSPECTIVES

In this observational study, more intensive management of hypertension improved blood pressure control to a similar extent regardless of the patient's level of adherence. The findings of this study do not diminish the importance of identifying patients with suboptimal adherence and trying to help them improve their adherence, because adherence remains an unquestioned determinant of control for hypertension and numerous other conditions. However, this study does call into question the widely held assumption that "nonadherent" patients cannot benefit from therapy intensification. Indeed, one of the major contributions of this study is to remind us that adherence is not a binary concept, with patients divided into those who are "adherent" or "nonadherent". Instead, all patients should be viewed as somewhere on a spectrum of adherence. The issue that we examined (i.e. whether patients with uncontrolled hypertension

and suboptimal adherence benefit from therapy intensification) has not previously been subjected to investigation because the answer was widely assumed. Now that this assumption has been challenged, we think it is time for further studies, particularly randomized trials, to determine the most effective management strategy for patients with uncontrolled hypertension and suboptimal adherence.

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**Table 1**

Baseline characteristics of the study population (n = 819).

| Characteristic | Percentage or Mean Value |
|---|---|
| Mean Age | 59.6 |
| Male Gender | 34% |
| Black Race | 58% |
| Current Smoker | 7% |
| Obese | 59% |
| Comorbid Conditions | |
| Benign Prostatic Hypertrophy | 4% |
| Cerebrovascular Disease | 6% |
| Chronic Heart Failure | 4% |
| Chronic Kidney Disease | 7% |
| Coronary Artery Disease | 13% |
| Diabetes | 33% |
| Hyperlipidemia | 54% |
| Peripheral Vascular Disease | 5% |
| Frequency of Clinic Visits | |
| Mean Person-Time, Months | 24.3 |
| Mean Clinic Visits | 12.0 |
| Mean Clinic Visits/Month | 0.49 |
| Medication Classes at Baseline | |
| ACE Inhibitors or ARBs | 65% |
| Beta Blockers | 45% |
| Calcium Channel Blockers | 36% |
| Diuretics, Thiazide or Loop | 65% |
| All Other Classes Combined | 12% |
| Baseline Number of Medications | |
| None | 1% |
| 1 | 25% |
| 2 | 37% |
| 3 | 25% |
| 4 or more | 13% |
| Baseline Blood Pressure Control | |
| Mean Baseline Blood Pressure, mm/Hg | 134/80 |
| Baseline Blood Pressure < 140/90 mm/Hg | 55% |

**Table 2**

Mean treatment intensity (TI) score after stratifying by quartiles of adherence to therapy.

| Group (% of days adherent) | N | Mean TI Score* |
|---|---|---|
| Best Adherence (> 98%) | 168 | −0.24 |
| Good Adherence (93%–98%) | 168 | −0.26 |
| Fair Adherence (80%–93%) | 173 | −0.26 |
| Worst Adherence (< 80%) | 162 | −0.33 |
| Missing Adherence | 148 | −0.33 |
| Test of Linear Trend | -- | 0.002 |

* Mean TI score for entire sample (n = 819) was −0.28. A difference of 0.1 in the TI score indicates one more therapy increase than predicted per 10 visits.

**Table 3**

Effect of treatment intensity score on final systolic blood pressure. Interaction terms were used to test whether the effect sizes in patients with suboptimal adherence differed from the effect size among patients in the top quartile of adherence. (n = 819)

| Adherence Group | Adjusted Effect* | p-value† |
|---|---|---|
| Best Adherence (>98%) | −2.1 | -- |
| Good Adherence (93%–98%) | −1.8 | 0.49 |
| Fair Adherence (80%–93%) | −2.3 | 0.73 |
| Worst Adherence (< 80%) | −2.4 | 0.55 |
| Missing Adherence | −1.6 | 0.22 |

*Analyses adjusted for demographics, comorbid conditions, and treatment assignment (intervention vs. control). All beta coefficients are expressed in mm/Hg. Effect of TI is per change of 0.1 in the treatment intensity score (equivalent to one additional therapy increase per 10 visits). For example, a beta coefficient of −2.0 means that for every additional therapy increase per ten visits, the mean final systolic blood pressure will be 2.0 mm/Hg lower.

†P-values for adherence strata test for a difference from the excellent adherence group. The effect of the entire TI variable was statistically significant ($p < 0.001$). In addition, when each adherence stratum was analyzed separately, the effect of TI was statistically significant.