The Association Between Medication Adherence and Treatment Intensification With Blood Pressure Control in Resistant Hypertension

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Abstract—Patients with resistant hypertension are at risk for poor outcomes. Medication adherence and intensification improve blood pressure (BP) control; however, little is known about these processes or their association with outcomes in resistant hypertension. This retrospective study included patients from 2002 to 2006 with incident hypertension from 2 health systems who developed resistant hypertension or uncontrolled BP despite adherence to ≥3 antihypertensive medications. Patterns of hypertension treatment, medication adherence (percentage of days covered), and treatment intensification (increase in medication class or dose) were described in the year after resistant hypertension identification. Then, the association between medication adherence and intensification with 1-year BP control was assessed controlling for patient characteristics. Of the 3550 patients with resistant hypertension, 49% were male, and mean age was 60 years. One year after resistance hypertension determination, fewer patients were taking diuretics (77.7% versus 92.2%; P<0.01), β-blockers (71.2% versus 79.4%; P<0.01), and angiotensin receptor blocker (64.8% versus 70.1%; P<0.01) compared with baseline. Rates of BP control improved over 1 year (22% versus 55%; P<0.01). During this year, adherence was not associated with 1-year BP control (adjusted odds ratio, 1.18 [95% CI: 0.94–1.47]). Treatment was intensified in 21.6% of visits with elevated BP. Increasing treatment intensity was associated with 1-year BP control (adjusted odds ratio, 1.64 [95% CI: 1.58–1.71]). In this cohort of patients with resistant hypertension, treatment intensification but not medication adherence was significantly associated with 1-year BP control. These findings highlight the need to investigate why patients with uncontrolled BP do not receive treatment intensification. (Hypertension. 2012;60:303-309.) ○ Online Data Supplement

Key Words: hypertension ■ resistant ■ adherence ■ intensification

Hypertension is the most common cardiovascular risk factor worldwide and uncontrolled blood pressure (BP) is associated with worse cardiovascular outcomes.1–4 Patients with resistant hypertension represent a subset of hypertensive patients whose BP remains uncontrolled despite the optimal use of ≥3 medications.5 It is generally believed that resistant hypertension patients are at even greater risks for poor outcomes compared with the general hypertension population.5,6 Therefore, BP control is even more important to achieve among patients with resistant hypertension; however, the factors associated with BP control have not been well described in this patient population.

Medication adherence and therapy intensification have been identified as important factors in achieving BP control in general hypertension populations.7–12 However, little is known regarding either therapy adherence or intensification among patients identified as having truly resistant hypertension based on the American Heart Association scientific statement.13,14 By definition, patients with resistant hypertension are already taking multiple antihypertensive medications increasing their risk for poor adherence and providers may be less likely to intensify therapy given limited therapeutic options.15 In addition, some studies have suggested that evidence-based and guideline-recommended antihypertensive

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classes, such as diuretics, may be underused among patients with resistant hypertension. Describing patterns of medication class use, medication adherence, and therapy intensification in a population of resistant hypertension patients is important for targeting future interventions aimed at improving hypertension outcomes.

Accordingly, among a cohort of patients with resistant hypertension treated within 2 large integrated healthcare delivery systems, we sought to describe their medication class use, medication adherence, and treatment intensification (TI) in the year after identification of resistant hypertension. Next, we assessed the relationship between treatment adherence and therapy intensification with subsequent BP control adjusting for patient and clinical characteristics. Understanding the relationship between these factors and hypertension control will inform interventions aimed at improving BP outcomes among patients with resistant hypertension.

**Methods**

**Study Population**

The study sample was identified from 2 health plans within the Cardiovascular Research Network hypertension registry from 2002 to 2006. The development of the Cardiovascular Research Network hypertension registry has been described in detail elsewhere. In brief, patients with hypertension at Kaiser Permanente Colorado and Kaiser Permanente Northern California were identified using a published algorithm consisting of International Classification of Diseases, 9th Revision, diagnosis codes, BP measurements (from nonurgent visits), and pharmacy data. The current analysis only includes patients with incident hypertension being started on antihypertensive medication who were subsequently identified as having resistant hypertension based on the American Heart Association definition. As described previously by our group in detail, incident hypertension was defined as being a member of the health plan for ≥1 year before meeting criteria for the registry without any previous diagnosis of hypertension and without any previous pharmacy dispensing for antihypertensive medications. Patients were then determined to have resistant hypertension based on their number of medications filled, BP measurements, and medication adherence data over the year after initiation of treatment. Those patients who continued to have uncontrolled BP despite ≥3 medications (or controlled on ≥4 medications) who were adherent to medications were deemed to have resistant hypertension. Patients who disenrolled from the health plan (n = 17), died (n = 53) within 12 months, or did not have ≥6 months of follow-up (n = 340) after the date that hypertension was determined to be resistant were excluded from this analysis. For this analysis, we followed patients for 1 year after the date that they were determined to have resistant hypertension to assess medication adherence, TI, and their association with 1-year BP control (see Figure S1 in the online-only Data Supplement).

**Medication Use and BP Information**

Medication dosing and class information were obtained from pharmacy dispensing databases. Medication classes studied included β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, diuretics (thiazide, K-sparing, loop and carbonic anhydrase inhibitor), α-adrenergic blockers, and peripheral vasodilators. For each medication, dosing was further characterized as the percentage of recommended maximum daily dose based on Micromedex 2.0 dosing information for the treatment of hypertension.

BP values were obtained from each patient’s electronic medical chart. To avoid spuriously high values, we excluded all of the measurements that occurred in an inpatient setting, on the day of a procedure (where BP medications may have been temporarily held) or during an emergency department visit (where pain or other emergent conditions may cause temporary elevations in BP). For this analysis, only systolic BPs (SBPs) were used, because resistant hypertension is most often attributed to uncontrolled SBP, and SBP has a stronger association with outcomes than diastolic BP.

**Medication Adherence**

Medication adherence was calculated as the proportion of days covered based on the number of days of BP medication supplied divided by the numbers of days in the observation interval. For patients receiving multiple BP medications, an average proportion of days covered was calculated across all medications. Patients with a summary adherence measure of >80% were considered adherent. We were unable to calculate a proportion of days covered on 2 patients who had insufficient medication supply and they were, therefore, excluded from this analysis.

**Treatment Intensification**

TI was calculated using a standard-based method score, as characterized by Rose et al. The TI score assesses the number of times that TI appropriately occurs. The TI score is calculated by taking the number of observed TIs minus the number of expected TIs divided by the number of clinic visits with SBP measurements over the observation period. For this analysis, we only included SBP measurements that occurred in specific departments (family practice, internal medicine, obstetrics/gynecology, cardiology, or nephrology) to avoid values measured in departments for which BP management is not a routine part of clinical practice. Observed TI was the number of times a previously prescribed antihypertensive medication dose was increased or an antihypertensive medication class was added in the 4 weeks after the occurrence of an elevated SBP. We allowed a grace period of 4 weeks after the measurement of an elevated SBP to allow for the clinical scenario when providers may be waiting for any previous TI to take effect before taking further clinical action or for a new medication dispensing to be started if patients are told to increase the dose of a previously dispensed medication. Expected TI was the number of visits when the measured SBP was elevated above the target goal. Accordingly, the TI score could range from −1.0 to +1.0, with −1 indicating no TI at any visit where the SBP was elevated, 0 indicating TI at every visit where the SBP was elevated, and 1 indicating TI at every visit regardless of the SBP level. Patients with missing follow-up BP information (n = 762 [21%]) were excluded from this analysis.

For all of the TI analyses, we assessed for TI only when the measured SBP was ≥5 mm Hg above the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure goal (ie, ≥135 mm Hg for patients with diabetes mellitus or renal disease or ≥145 mm Hg for all others) to account for potential clinical ambiguity in intensifying therapy when the SBP is only a few millimeters of mercury above the target goal.

**Outcome**

The outcome of interest was SBP control based on the BP occurring closest to 1 year after meeting resistant hypertension criteria. In the primary analysis, elevated SBP was defined according to the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure thresholds of SBP ≥140 mm Hg with lower cutoffs of SBP ≥130 mm Hg for those with diabetes mellitus or chronic kidney disease. In secondary analysis, we increased the cutoffs of SBP to define the outcome of BP control by 5 mm Hg (SBP <145 mm Hg or SBP <135 mm Hg for those with diabetes mellitus or chronic kidney disease).

**Statistical Analysis**

Baseline characteristics of all of the patients with resistant hypertension were described using frequencies, means, and medians. Medication class use at baseline and follow-up were compared using χ² tests. Finally, for each patient, the averaged percentage of recom-
mended maximal daily dosing for their antihypertensive medications was compared at baseline and follow-up using the paired \( t \) test.

In the primary outcome analysis, multivariable logistic regression models assessed the association between adherence and TI with subsequent BP control 1 year after resistant hypertension identification adjusting for patient demographics, coexisting conditions, year of cohort entry, study site, BP at time of resistance status determination, and number of BPs over follow-up. Patients without a BP measurement within 455 days of resistance status determination (\( n=762 \) [21%]) were excluded from the outcomes analysis. In additional analysis, based on previous literature suggesting variations in BP control in certain groups, we investigated whether SBP control varied significantly among the prespecified subgroups of sex, race, diabetes mellitus, chronic kidney disease, and medication class.1,23–29

All of the analyses were performed using the SAS statistical package version 9.2 (SAS Institute, Inc, Cary, NC). The study was approved by the institutional review board of both health plans.

Results
Of the 3550 patients with resistant hypertension, 49% were men, 61% were white, and the median age was 60 years (25th quartile, 51 years; 75th quartile, 70 years). The most common comorbidity was diabetes mellitus (17%), followed by depression (9%) and asthma (9%; Table 1). Compared with their antihypertensive regimen at the time of being classified as having resistant hypertension, 1 year later fewer patients were taking diuretics (77.7% versus 92.2%; \( P<0.01 \)), \( \beta \)-blockers (71.2% versus 79.4%; \( P<0.01 \)), angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (64.8% versus 70.1%; \( P<0.01 \)), and adrenergic blockers (12.5% versus 13.4%; \( P=0.02 \)). The use of calcium channel blockers (35.2% versus 35.4%; \( P=0.85 \)) and peripheral vasodilators (3.0% versus 2.9%; \( P=0.91 \)) did not significantly change from baseline to follow-up. On average, at baseline patients were taking 38.4% (95% CI, 37.8% to 39.0%) of maximal recommended daily dosing compared with 43.2% of maximal recommended daily dosing (95% CI, 42.4% to 43.9%) for hypertension 1 year later (\( P<0.0001 \) for comparison).

Medication Adherence
Over the year after resistance status determination, median medication adherence rates were 84.7% (25th quartile, 68.5%; 75th quartile, 94.9%) among the 3548 patients with medication refill information. More than half of patients (57.6%) met our criteria for medication adherence by achieving a summary adherence measure of >80%.

Treatment Intensification
Among the 2788 patients with resistant hypertension who had follow-up BP information, there were 13653 visits (median visits per patient, 4) in which BP was measured in the year after resistant hypertension identification. Almost all (99.5%) of these visits were in primary care (family practice, internal medicine, or obstetrics/gynecology), with the remaining visits occurring in cardiology. The majority (84.6%) of patients had \( \geq1 \) visit with an elevated BP over the follow-up period (median number of visits with an elevated BP per patient, 2). TI (class addition or dosage increase) occurred in only 21.6% of visits with an elevated BP. Of the 2788 patients in the analysis, 10% of patients had a class addition and 32% had a dose increase. The median TI score was −0.43 (25th quartile, 0.91) did not significantly change from baseline to follow-up. On average, at baseline patients were taking 38.4% (95% CI, 37.8% to 39.0%) of maximal recommended daily dosing compared with 43.2% of maximal recommended daily dosing (95% CI, 42.4% to 43.9%) for hypertension 1 year later (\( P<0.0001 \) for comparison).

### Table 1. Characteristics of Cohort at the Time of Resistant Hypertension Identification

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>3550</td>
</tr>
<tr>
<td>Sex, %</td>
<td>49.4</td>
</tr>
<tr>
<td>Male</td>
<td>50.6</td>
</tr>
<tr>
<td>Race, %</td>
<td>81.7</td>
</tr>
<tr>
<td>White</td>
<td>18.3</td>
</tr>
<tr>
<td>Black</td>
<td>17.9</td>
</tr>
<tr>
<td>Missing</td>
<td>10.0</td>
</tr>
<tr>
<td>Site, %</td>
<td>10.0</td>
</tr>
<tr>
<td>Kaiser Northern California</td>
<td>94.4</td>
</tr>
<tr>
<td>Kaiser Colorado</td>
<td>5.6</td>
</tr>
<tr>
<td>Year of hypertension registry entry, %</td>
<td>10.0</td>
</tr>
<tr>
<td>2000</td>
<td>2.7</td>
</tr>
<tr>
<td>2001</td>
<td>16.2</td>
</tr>
<tr>
<td>2002</td>
<td>38.6</td>
</tr>
<tr>
<td>2003</td>
<td>20.3</td>
</tr>
<tr>
<td>2004</td>
<td>12.1</td>
</tr>
<tr>
<td>2005</td>
<td>7.1</td>
</tr>
<tr>
<td>2006</td>
<td>3.0</td>
</tr>
<tr>
<td>Baseline comorbidities, %</td>
<td>10.0</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>0.7</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>3.5</td>
</tr>
<tr>
<td>Angina</td>
<td>0.8</td>
</tr>
<tr>
<td>Asthma</td>
<td>9.3</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.8</td>
</tr>
<tr>
<td>Bipolar</td>
<td>0.6</td>
</tr>
<tr>
<td>Coronary artery bypass</td>
<td>0.7</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.8</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>5.0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17.4</td>
</tr>
<tr>
<td>Depression</td>
<td>9.4</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.5</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.9</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>2.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.5</td>
</tr>
<tr>
<td>Hypertension medications, %</td>
<td>30.0</td>
</tr>
<tr>
<td>( \beta )-blockers</td>
<td>79.4</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>70.1</td>
</tr>
<tr>
<td>Diuretics</td>
<td>92.2</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>35.4</td>
</tr>
<tr>
<td>Alpha adrenergic blocker</td>
<td>13.4</td>
</tr>
<tr>
<td>Peripheral vasodilators</td>
<td>3.0</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure.
Among patients included in the primary outcomes analysis (n=2788), BP control improved from the time of resistant hypertension identification to 1 year of follow-up (22% versus 55%; \( P<0.01 \)). In the unadjusted analysis, medication adherence was marginally associated with BP control (odds ratio [OR] 1.21 [95% CI, 1.00–1.47]; \( P=0.05 \)). In the fully adjusted model, the association between medication adherence and BP control was no longer significant (adjusted OR, 1.18 [95% CI, 0.94–1.47]; \( P=0.15 \)).

In unadjusted analysis, increasing BP treatment intensity was significantly associated with better BP control. For each 0.1 increase in the TI score (indicating more intensive BP treatment), the odds of having controlled BP at 1 year increased by 60% (OR, 1.60 [95% CI, 1.54–1.66]; \( P<0.01 \)). This relationship persisted in the multivariable models (OR, 1.64 [95% CI, 1.58–1.71]; \( P<0.01 \)). In secondary analysis using a higher BP cutoff to define control (<135 mm Hg for diabetes mellitus and chronic kidney disease and <145 mm Hg for all others), increasing TI remained significantly associated with BP control (OR, 1.66 [95% CI, 1.59–1.73]; \( P<0.01 \)).

In additional analysis, evaluating factors associated with BP control among resistant hypertension patients, sex (\( P=0.59 \)), race (\( P=0.46 \)), diabetes mellitus (\( P=0.71 \)), and chronic kidney disease (\( P=0.25 \)) were not associated with BP control (Table 2). With regard to medications class use 1 year after resistance status determination, use of an angiotensinogen-converting enzyme inhibitor/angiotensin receptor blocker, calcium channel blocker, or alpha-adrenergic blocker was associated with less BP control (OR, 0.88 [95% CI, 0.71–1.10]; \( P=0.27 \)). The majority of resistant hypertension patients were adherent to their antihypertensive medications and, on average, they received less than expected TI over the 1 year of follow-up. TI, but not therapy adherence, was significantly associated with 1-year BP control.

Despite recognition of the importance of resistant hypertension by the American Heart Association and others, this group of patients has been relatively poorly described.5,6,14,30–32 Our study expands the current literature by including our ability to longitudinally follow patients using detailed medication and clinical information, allowing a description of medication adherence and therapy intensification and their association with BP control.

In the current study, we have shown that the use of many classes of antihypertensive medications decreases 1 year after resistant hypertension identification. Importantly, one of the largest declines was in diuretic use; >90% of the patients prescribed any diuretic at baseline, but only 78% remained on a diuretic 1 year later (\( P<0.01 \)). Patients with resistant hypertension are thought to have inappropriate

### Table 2. Predictors of 1-Year Blood Pressure Control Among Patients With Resistant Hypertension

<table>
<thead>
<tr>
<th>Effect</th>
<th>Adjusted OR (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment intensification score (per 0.1 unit)</td>
<td>1.64 (1.58–1.71)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Adherent vs nonadherent (≥80% PDC)</td>
<td>1.18 (0.94–1.47)</td>
<td>0.15</td>
</tr>
<tr>
<td>No. of blood pressures over follow-up</td>
<td>0.99 (0.97–1.01)</td>
<td>0.37</td>
</tr>
<tr>
<td>Medication classes at time of outcome BP status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>0.74 (0.59–0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diuretic thiazide, loop, CAI, or K-sparing</td>
<td>1.64 (1.27–2.12)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>K-sparing diuretic only</td>
<td>0.81 (0.62–1.08)</td>
<td>0.15</td>
</tr>
<tr>
<td>( \beta )-blocker</td>
<td>0.88 (0.71–1.10)</td>
<td>0.27</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>0.79 (0.64–0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>Alpha 1 and 2 adrenergic blocker</td>
<td>0.70 (0.52–0.94)</td>
<td>0.02</td>
</tr>
<tr>
<td>Other (peripheral vasodilator and reserpine)</td>
<td>0.75 (0.44–1.27)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Demographics

- Sex, male vs female: 0.95 (0.77–1.16) \( P=0.59 \)
- Race: 0.46
- Black vs white: 1.16 (0.81–1.66) \( P=0.94 \)
- Missing vs white: 0.92 (0.64–1.31) \( P=0.63 \)
- Other vs white: 0.87 (0.69–1.11) \( P=0.25 \)
- Smoking status, current vs not: 0.99 (0.70–1.38) \( P=0.94 \)
- Age at index in y: 1.00 (0.90–1.10) \( P=0.74 \)
- Hypertension registry entry year: 1.10 (1.02–1.19) \( P=0.02 \)

Baseline comorbidities

- Albuminuria: 0.85 (0.29–2.48) \( P=0.76 \)
- Alcohol abuse: 1.25 (0.73–2.12) \( P=0.42 \)
- Angina: 2.01 (0.70–5.79) \( P=0.19 \)
- Asthma: 1.03 (0.74–1.42) \( P=0.87 \)
- Atrial fibrillation: 1.17 (0.66–2.05) \( P=0.59 \)
- Bipolar: 1.33 (0.38–4.68) \( P=0.66 \)
- Chronic kidney disease: 0.78 (0.51–1.20) \( P=0.25 \)
- Diabetes mellitus: 0.96 (0.75–1.22) \( P=0.71 \)
- Depression: 1.08 (0.77–1.51) \( P=0.65 \)
- Migraine: 1.29 (0.66–2.53) \( P=0.46 \)
- Other arrhythmias: 0.93 (0.45–1.91) \( P=0.85 \)
- Peripheral vascular disease: 1.34 (0.69–2.60) \( P=0.39 \)
- Schizophrenia: 1.03 (0.18–5.84) \( P=0.98 \)
- Sleep apnea: 1.56 (0.74–3.26) \( P=0.24 \)

\( \text{ACE} \) indicates angiotensin-converting enzyme inhibitor; \( \text{ARB} \), angiotensin receptor blocker; \( \text{BP} \), blood pressure; \( \text{OR} \), odds ratio; \( \text{CAI} \), carbonic anhydrase inhibitor; \( \text{PDC} \), proportion of days covered.
volume expansion and, therefore, the American Heart Association criteria for resistant hypertension state that these patients should ideally be on a diuretic. In fact, studies have shown that optimizing diuretic therapy was the most common means of improving BP control in patients with resistant hypertension. Similarly, we have demonstrated that diuretic use tended to be associated with improved BP control (OR, 1.64 [95% CI, 1.27–2.12]). Taken together, these studies support the importance of treating patients with resistant hypertension with diuretics, and future work should investigate why some patients were no longer filling this important class of medications.

Another important finding of this study is the persistently low rates of BP control seen among resistant hypertensive patients. Only 55% of patients had their BP controlled 1 year after resistant hypertension identification. In another cohort (n=141) of patients referred to a hypertension subspecialty clinic, Garg et al similarly reported that 53% of patients identified as having resistant hypertension subsequently had their BP controlled. Identifying low rates of hypertension control among a resistant hypertension population is significant, because poor BP control is associated with worse cardiovascular outcomes. Understanding potential contributors to poor BP control in this population is a crucial first step to potentially improve their outcomes.

Our study is one of the first to investigate both medication adherence and TI and their relationships with BP control in a broad population of patients with resistant hypertension. Overall, the majority of our patients with resistant hypertension were adherent (median adherence, 85%) to their antihypertensive medications over 1 year of follow-up. In accordance with the American Heart Association definition of resistant hypertension, we purposely selected a population of patients with “true” resistant hypertension excluding patients who were deemed to have “pseudoresistant” hypertension or uncontrolled BP attributed to poor medication adherence in the year before entry. Importantly, 1 year later, 42% of patients in our study cohort no longer met criteria for high adherence (>80% proportion of days covered), suggesting that significant drops in adherence occurred in a previously adherent group. These findings highlight the importance of continued monitoring of adherence and suggest that, as regimens become more complex, patient adherence may decline. Overall, we found no significant association between patient medication adherence and eventual BP control. Another study of 44 patients with true resistant hypertension found high rates of medication adherence (94%) over follow-up and no significant association between medication adherence and subsequent BP control. Together, these findings suggest that poor BP control in true resistant hypertension patients is not largely attributed to their failure to take medications.

One of the most important findings of our study is an investigation of appropriate therapy intensification among resistant hypertensive patients. Over 1 year of follow-up, the average patient with resistant hypertension received less than expected intensification of either their medication class or dose despite having opportunities for intensification (BP visits) and documentation of elevated BPs. Garg et al similarly found that a suboptimal medication regimen was common, accounting for 57% of those referred to their subspecialty clinic for resistant hypertension. In this same study, the largest improvement in hypertension control was seen among those whose BP medications were optimized over follow-up. Similarly, we have shown a significant relationship between increasing degrees of TI and subsequent BP control, further supporting the importance of medication intensification for achieving BP control in this population.

Based on the literature from general hypertension populations, potential reasons for less than expected TI in our study may include clinical inertia and competing demands of comorbid conditions. Another potential reason for less than expected TI may be that BP levels were considered to be “close enough” to control levels. In secondary analysis, we allowed higher cutoff values of SBP to define BP control and found similarly lower than expected degrees of TI. Failure to intensify therapy may also be related to a lack of evidence to support the efficacy of adding additional agents to those already on ≥3 antihypertensive classes. This lack of evidence may in part contribute to therapeutic nihilism or skepticism about the benefit of intensifying therapy in patients who are already taking multiple antihypertensives. However, we also demonstrated that, on average, patients were taking <50% of the recommended maximal daily doses of their antihypertensive medications at follow-up suggesting room for dosage increases that do not require a class addition. Our findings highlight the importance of therapy intensification to improve BP control in patients with resistant hypertension, suggesting practitioners should attempt to optimize therapy in this population at high risk for poor cardiovascular outcomes.

Certain limitations should be considered in the interpretation of the study results. First, this study relies on BP measurements from an electronic medical chart. However, we have shown that the algorithms used to identify hypertensive patients were valid, and the analytic data accurately reflect the data in the charts. In addition, office-based BP measurements reflect current practice and are used routinely in the management of hypertension. Second, our medication adherence and TI estimations rely on pharmacy refill information. Similar to other studies using pharmacy dispensing data, we assumed that dispensed medications were consumed if the prescription was refilled but could not determine whether prescribed medications were filled or if medications orders were discontinued. However, pharmacy refill data are correlated with a broad range of clinical outcomes. In addition, the act of refilling a medication is the necessary first step toward taking a medication and reflects the patients’ active decision to continue with therapy. Finally, the findings in these integrated healthcare systems may not apply to other healthcare settings. However, these 2 systems care for ~4 million patients in geographically distinct areas, and our population was drawn from an ambulatory population of hypertension patients seen in both primary care and subspecialty clinics.

**Perspectives**

In this cohort of patients with resistant hypertension, TI but not medication adherence was significantly associated with 1-year BP control. Overall, the findings of this study have
several clinical and research implications. First, rates of BP control for patients with resistant hypertension were lower: ≈ 1 in 2 patients with resistant hypertension met BP targets 1 year after identification. Given their higher risk for poor outcomes, efforts to improve control rates among this high-risk population are important for preventing cardiovascular disease. Second, patients with resistant hypertension appear to have at least average medication adherence and, unlike other hypertension populations, poor adherence does not appear to contribute to low rates of BP control. Third, lower than expected TI was significantly associated with poor BP control. Therefore, system changes directed at improving BP control among patients with resistant hypertension should devote attention to understanding and improving appropriate TI.

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Disclosures
None.

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### Novelty and Significance

#### What Is New?
- This is one of the first studies to investigate the relationship between medication adherence and treatment intensification (TI) with blood pressure control among a large population of patients with resistant hypertension identified within both general and subspecialty clinics.

#### What Is Relevant?
- Patients with resistant hypertension are at high risk for poor outcomes.
- Understanding potential causes of uncontrolled blood pressure in these high-risk patients will help direct future efforts to improve their outcomes.

#### Summary
- TI but not medication adherence was significantly associated with improved blood pressure control.
- Studies are needed to better understand and improve lower than expected TI among patients with resistant hypertension.
The Association Between Medication Adherence and Treatment Intensification With Blood Pressure Control in Resistant Hypertension

Stacie L. Daugherty, J. David Powers, David J. Magid, Frederick A. Masoudi, Karen L. Margolis, Patrick J. O’Connor, Julie A. Schmittdieu and P. Michael Ho

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Resistant HTN Identified N=3,550

1-Year

Primary Predictors:
1. Medication Adherence
2. Treatment Intensification

Primary Outcome:
Blood Pressure Control

S1: Diagram of study population, primary predictors and primary outcomes.