Editorial

Recommendations for Evaluating Compliance and Persistence With Hypertension Therapy Using Retrospective Data


Hypertension is a major risk factor for cardiovascular and cerebrovascular disease. The World Health Organization Global Burden of Disease Study estimates that nonoptimal blood pressure [(BP) ie, systolic BP of >115 mm Hg] is responsible annually for 7.1 million deaths and the loss of 64.3 disability-adjusted life years worldwide.1 The associated economic burden of hypertension is also substantial. The average annual medical care cost for individuals with hypertension has been estimated at $3900 (in year 2000 US dollars) in Canada,2 with similar values ($3787) for the United States.3 The increase in medical care costs is greater for those with moderate-to-severe BP elevation (diastolic BP >104 mm Hg) than for those with milder disease.4

Although a broad range of hypertension medications have been demonstrated to reduce BP, and BP control is an achievable goal,5 reports suggest that up to two thirds of patients with hypertension are not successfully treated, that is, achieve BP control.6–8 According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7), BP control rates are far below the “healthy people” goal of 50% set in 2000.9 A major (and modifiable) reason for lack of BP control is failure by patients to use medications as prescribed.10 Appropriate use of medications includes compliance, taking medications at the prescribed frequency/interval and dose/dosing regimen, and persistence, continuing their use for the specified treatment time period, which, in the case of hypertension therapy, is usually lifelong.11 Poor compliance with hypertension medications is associated with adverse health outcomes.12

Studies have demonstrated that poor BP control is associated with greater healthcare costs.13 For example, in the United States, inadequate control of hypertension has been estimated to result in ≈40 000 cardiovascular events, >8000 cardiovascular disease deaths, and approximately $964 million in direct medical expenditures.14 Similarly, poor compliance and lack of persistence with BP medications are associated with increased health care costs.15,16 Whereas patients who interrupted hypertension therapy had decreased medication costs, they had greater increases in costs for other health care, mainly reflecting increased hospital costs.17 In other disease states, such as diabetes and hypercholesterolemia, whereas increased compliance is associated with increased medication costs (because compliant patients use more medication), overall health care costs decrease because of better disease control and lower rates of adverse outcomes.18

Compliance and persistence can be measured in both retrospective and prospective studies, both of which can provide data on “real world” clinical practice. However, participants in prospective evaluations may not be comparable to broader patient populations. Furthermore, prospective evaluations can potentially introduce biases, particularly in patient behaviors related to compliance and persistence. Although the use of retrospective databases avoids these problems, the lack of consistent methods for evaluation of hypertension treatment compliance and persistence in such studies makes comparisons of results among studies difficult. As presented in a review by Lopatriello et al,19 this lack of standardization in study design, population, and methods can produce tremendous variations in reported compliance with hypertension therapy. In addition, the lack of broadly agreed-on methods creates substantial barriers for evaluating the potential impact of compliance and persistence on BP control. Given the importance of this issue, we have developed a set of recommendations for retrospective studies assessing compliance and persistence in hypertension.

Importance of Hypertension Therapy Compliance and Persistence in Medical Practice

Noncompliance is usually considered as missing medication doses in the context of ongoing use, whereas nonpersistence refers to premature discontinuation of treatment. Although compliance and persistence are both components of appropriate medication use, they have differing implications for medical practice. Lack of persistence often occurs when patients discontinue therapy without instructions from or...
even discussions with their physicians. This may occur early in a course of therapy, reflecting adverse effects associated with (or perceived to be associated with) a new drug treatment. As a result, patients will not be receiving hypertension treatment and are at increased risk for sequelae associated with elevated BP. Whereas patients who rapidly achieve target BP generally show increased persistence,20 patients who do not achieve BP control (that is, do not reach systolic BP <140 and diastolic BP <90 mm Hg, as defined by JNC-7)20 or those who experience adverse effects may be tempted to modify their medication doses,8 and there are generally no immediate symptomatic consequences of doing so. Furthermore, the prescribing physician may assume that the resulting lack of BP control is because of a lack of medication effectiveness rather than lack of medication use and respond by inappropriately intensifying the medication regimen.

In contrast, lack of compliance generally occurs in the context of ongoing treatment, when patients modify their dosing rather than discontinue therapy completely. Thus, the effects of noncompliance may be less overt; observed changes in BP may be less dramatic than those seen with nonpersistence. However, this lack of BP control will also increase patients’ risk of cardiovascular and related sequelae and lead physicians to assume inadequate effectiveness of the medication(s) being used. Physicians may also overestimate patient compliance with BP therapy.21 This may result in physicians being less likely to ask patients about their compliance with therapy or to stress the importance of treatment compliance with patients.

As discussed by the World Health Organization,22 factors contributing to lack of compliance and/or persistence are in 5 categories: patient-related, condition-related, therapy-related, health system, and socioeconomic factors. Condition-related factors are particularly important in evaluating compliance and persistence with hypertension therapy. Hypertension is largely asymptomatic, and patients often have little understanding of the importance of achieving BP control.23 Given the lack of symptoms, medication adverse effects become an important factor in noncompliance and nonpersistence24–26; noncompliance has been reported to increase with any adverse effects and with increasing numbers of adverse effects.27 In addition, although there are cases in which lifestyle changes, weight loss, or correction of secondary causes of hypertension have reduced or eliminated the need for pharmacological therapy, more often treatment is lifelong.

### Types of Databases

Studies of compliance and persistence with hypertension medications can be performed using a variety of databases, ranging from those containing only pharmacy data to data sets incorporating electronic medical records with comprehensive claims information. Ideally, retrospective assessments of compliance, persistence, and treatment outcomes in hypertension should be performed using databases with diagnosis information so that patients with hypertension can be appropriately identified, whereas those receiving hypertension medications for other indications (eg, patients receiving diuretics for treatment of edema associated with heart failure or calcium channel blocker therapy for angina) can be excluded. Databases used for retrospective studies will also ideally contain complete medical resource use information, as well as clinical data including BP readings. Records of medical resource use (eg, medication prescriptions, outpatient visits, hospitalizations, and diagnostic and laboratory procedures) will permit assessments of treatment patterns and associated costs for hypertension. The presence of BP readings and other clinical data will provide the necessary information for evaluations of short-term clinical outcomes (ie, change in BP) associated with compliance, persistence, and treatment patterns.

However, comprehensive databases with diagnosis information and clinical data are not always available. Although other types of databases can also be used for evaluations of compliance and persistence, the types of questions that can be addressed vary with the types of data available. This is summarized in Table 1.

A number of databases include only prescription information or prescription and other resource use data but no diagnoses (eg, a pharmacy benefit management database). These databases can be used to assess patterns of prescription refills, but the diagnosis of hypertension (as discussed below in the Desired Information section) is presumed based solely on the use of a hypertension medication. An advantage of prescription databases is that they tend to be very large and, thus, are useful for exploring previously developed hypotheses or confirming previous observations regarding the relationship of compliance/persistence to specific medications, medication types, or patient characteristics. However, they can be used only for very limited outcomes studies, because most outcomes of interest (including overall medical care costs) are generally not present.

<table>
<thead>
<tr>
<th>Database Type</th>
<th>Main Limitation</th>
<th>Advantages</th>
<th>Applicable Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claims without diagnosis codes</td>
<td>Cannot specifically identify hypertension patient</td>
<td>Often includes large numbers of patients</td>
<td>Patterns of prescription refills for drugs used to treat hypertension</td>
</tr>
<tr>
<td>Claims and diagnosis codes but no BP data</td>
<td>Cannot evaluate blood pressure control</td>
<td>Can identify hypertension and its sequelae; widely available</td>
<td>All except assessment involving treatment efficacy as measured by BP control</td>
</tr>
<tr>
<td>Claims, diagnosis codes, and clinical data including BP values</td>
<td>Few such databases are available; may correspond to a very specific population</td>
<td>Complete patient data</td>
<td>All</td>
</tr>
</tbody>
</table>
Databases with diagnosis information but without clinical data (eg, Medicare data and data from most managed care organizations) can be used for most outcomes and economic evaluations related to compliance and persistence. The presence of diagnoses allows for proper identification of the relevant patient groups and exclusion of patients receiving hypertension medications for other indications. The presence of diagnoses also permits identification of clinical outcomes associated with hypertension, such as myocardial infarctions. Furthermore, diagnoses will allow evaluations to control for concomitant conditions and to explore clinical outcomes in patient subgroups. However, the lack of BP readings and other detailed clinical information in such databases prevents assessment of the short-term effectiveness of hypertension therapy. That is, diagnostic codes will not specify whether or not a patient diagnosed with hypertension has controlled BP. Retrospective information can also be collected from medical chart review. However, whereas charts may contain information on BP readings and medication persistence, they are unlikely to include data on compliance. Furthermore, missing or incomplete data from medical charts are often problematic. Although missing data are also potential problems for claims databases, because these databases are often developed for reimbursement or billing purposes, they are less likely to have missing information regarding billable/reimbursable medical care.

Study Population

Evaluations of hypertension therapy often involve defining inception cohorts, that is, groups of individuals who are assessed from the point of therapy initiation. This provides for uniform populations with respect to the therapy being evaluated. In contrast, if patients are included in analyses at treatment points other than the time of therapy inception (eg, inclusion of some patients who began therapy months or years before their inclusion in analyses), the analysis populations will likely be highly heterogeneous, creating additional difficulties in assessing the impacts of treatment. Furthermore, patients who received the medications being evaluated before inclusion in the study (ie, prevalent patients) may have compliance and persistence values that are not generalizable to those of patients who are newly initiating therapy. Prevalent patients can be used in other specified types of evaluations, such as the impact of add-on therapy on compliance and persistence, but should not be included in inception cohort analyses.

To determine whether patients are truly new to a given therapy (ie, appropriate members of the inception cohort) and to assess patient characteristics before initiation of specific hypertension medications, a period of data collection before initiation of treatment with the medications being studied is required. During this period before initiation of the therapy or therapies of interest (ie, the study drug or drugs), patients may have received hypertension medications other than those being evaluated or may receive no hypertension medications. Similarly, data covering a substantial period of time after treatment initiation are needed to assess compliance and persistence. Therefore, we recommend that only patients with ≥6 months of data before their index date (defined as the date of the first prescription of the study drug within the study window) and 12 months of data after their index date should be included in the analysis. These minimum inclusion periods will allow for comparability between studies, in terms of excluding prevalent patients [ie, those who have received the study medication(s) in the previous 6 months] and controlling for preexisting medical conditions and other medication use (from the pretreatment period), as well as examining compliance, persistence, and rates of resource use and outcomes (from the posttreatment period). The recommended 6- and 12-month periods are compromises, maintaining a balance between maintaining study cohorts as large as possible and having sufficient information to appropriately analyze these cohorts. If data are available, longer periods before the index date (eg, 12 months) can be included to more fully characterize the study populations and to adjust for potential confounding.

Patients with no prescriptions for any hypertension medications in the 6-month period before the index date should be considered newly treated patients, whereas those who received other hypertension drug prescriptions (that is, other than the specific study drug or drugs) in this 6-month period should be considered established patients. These groups are clearly disparate, because newly diagnosed hypertension patients beginning their first course of medication are likely to have substantially different behaviors and responses to medication than are those who have not been successfully controlled on multiple courses of therapy. However, whereas established (ie, previously treated) hypertension patients with no prescriptions for the study medication(s) in the 6-month–prior period are not truly new users, they do not have established use patterns with the study medication(s). Thus, established patients who have not used the study medication(s) for ≥6 months are likely to be similar to true new users in terms of compliance and persistence, because they will need to develop new behaviors associated with taking the medication(s).

To be included in the analysis, patients must receive ≥2 prescriptions of the study drug without discontinuation (as discussed below in the Determination of Compliance and Persistence section) between them. Whereas data from patients who have received only 1 prescription may be useful for evaluating medication adverse effects (and short-term discontinuation of therapy because of lack of tolerance), receipt of a single, isolated prescription does not provide sufficient information for determination of either compliance or persistence. In addition, receipt of a single prescription for a hypertension drug does not indicate that a patient is taking the medication. The presence of a second prescription within 60 days of completion of the medication supply from the first prescription (ie, without discontinuation between the 2 prescriptions) suggests that the patient has consumed at least some medication from the first prescription. The criteria used to identify patients in retrospective data for hypertension compliance and persistence studies are summarized in Table 2.

Minimum Required Information

Patient Characteristics

A number of patient characteristics are associated with compliance and persistence. For example, younger patients
have been reported to have decreased compliance\(^2&^{28}\) and decreased persistence.\(^2&^{29,30}\) Race/ethnicity is also associated with hypertension therapy compliance, with compliance lower in nonwhites than whites.\(^3&^{31,32}\) Gender has not, in general, been reported to be associated with compliance,\(^3&^{33}\) although there are conflicting reports in the literature.\(^2&^{29,30}\)

When evaluating compliance or persistence, it is, therefore, necessary to characterize the study population based on age, gender, race/ethnicity, and other available demographic characteristics.

### Treatment History

Treatment history (ie, previous use of BP and other medications) affects medication compliance and persistence in hypertension. However, reports on the impact of treatment history on compliance and persistence are contradictory. A number of studies have reported that patients who have failed previous courses of therapy are likely to have lower compliance and persistence than do those who are newly treated or have been successful with previous therapy.\(^1&^{3,34}\) For example, patients naïve to treatment may have greater compliance because of heightened awareness of their new hypertension diagnosis.\(^3&^{35}\) Other studies have reported that persistence is greater for established hypertension patients than for newly diagnosed patients,\(^2&^{29}\) potentially reflecting that established patients have passed the stages of lack of belief in their hypertension diagnosis.\(^3&^{35}\) Studies of compliance and persistence (or comparisons of these measures across studies) should involve populations with relatively homogeneous treatment histories or control for differences in treatment histories. Analyses should be stratified for new versus established patients, or the 2 groups should be compared separately. Because knowledge of patients’ entire treatment history is not likely to be available, study selection criteria must be specified to identify patient populations with comparable treatment histories. For example, criteria can be used to identify patients not previously treated for hypertension (or who are using a first-line therapy) versus those who are using a medication reserved for second- or third-line treatment.

### Hypertension Medication Regimen and Concomitant Medication Use

Compliance is strongly affected by the frequency (number of times) a medication must be taken each day.\(^3&^{36}\) Compliance is greatest for patients receiving once-daily medications compared with medications taken ≥2 times (doses) per day. Results from a meta-analyses\(^3&^{37}\) and a systematic review\(^3&^{38}\) of compliance to hypertension therapy indicated similar findings, that compliance with twice-daily medication decreased by ~6% compared with compliance with once-daily medications. Similarly, compliance and persistence are greater among patients receiving 1 hypertension medication per day compared with those receiving ≥2 separate medications per day.\(^3&^{39,40}\) Compliance is also decreased among individuals receiving concurrent drug therapies for other chronic conditions.\(^4&^{41}\) For example, Chapman et al\(^4&^{42}\) reported that among patients receiving both hypertension and lipid-lowering therapy, only one third was compliant with both therapies at 6 months. Compliance with differing doses taken in the same day may also vary; Würzner et al\(^4&^{43}\) reported that compliance to hypertension medications taken in the evening is lower than that for medications taken in the morning. Thus, the frequency and number of medications taken per day on a regular basis must be included in the assessments. As discussed below (in the Determination of Compliance and Persistence section), combination agents (that is, single pills containing multiple active medications) should be considered as only 1 medication, because the behaviors and burdens related to these will not differ from those for a single pill with only 1 active ingredient.

### Desired Information

The desired information for studies of hypertension compliance and persistence are summarized in Table 3.

### Hypertension Diagnosis

As discussed above in the Types of Databases section, whereas data sets containing only pharmaceutical claims can be used to evaluate medication compliance and persistence, such evaluations are limited by the lack of diagnostic information. For evaluations of compliance and persistence in

### TABLE 2. Identification Criteria for Retrospective Study Populations

<table>
<thead>
<tr>
<th>Identification Criteria</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>No previous use of drug of interest in past 6 months (inception cohort)</td>
<td>Homogeneous population with respect to being “new starts” on therapy</td>
</tr>
<tr>
<td>Data for ≥6 months before index date</td>
<td>Control for patient characteristics before treatment initiation</td>
</tr>
<tr>
<td>Data for ≥12 months following index date</td>
<td>Evaluate compliance, persistence, and outcomes over a reasonable minimum period</td>
</tr>
<tr>
<td>≥2 prescriptions for drug of interest, with no discontinuation between prescriptions</td>
<td>Confirmation of use of drug beyond a single prescription; ability to calculate MPR</td>
</tr>
</tbody>
</table>

### TABLE 3. Desired Study Data

<table>
<thead>
<tr>
<th>Data</th>
<th>Purpose</th>
</tr>
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<tbody>
<tr>
<td>Hypertension diagnosis: confirmed (elevated BP readings or diagnosis code for hypertension)</td>
<td>Identify patients with definite hypertension</td>
</tr>
<tr>
<td>Hypertension diagnosis: presumed (use of hypertension medications and no diagnoses for other conditions indicated for the medications)</td>
<td>Identify patients likely to have hypertension</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td>Control for other factors affecting compliance, persistence, and outcomes; evaluate patient subgroups</td>
</tr>
<tr>
<td>Geography and health plan</td>
<td>Control for settings and potential restrictions on medication choice</td>
</tr>
<tr>
<td>BP</td>
<td>Assess treatment effectiveness and potential rationale for treatment changes</td>
</tr>
<tr>
<td>Weight and height</td>
<td>Incorporate effects of obesity on hypertension treatment outcomes</td>
</tr>
</tbody>
</table>
hypertension, it is necessary to establish that study subjects actually have hypertension, because many hypertension medications are also used for other indications. Patients with hypertension can be identified using 2 approaches, described below.

**Confirmed Diagnosis of Hypertension**

Claims with ICD-9 diagnosis code 401 or ICD-10 code I10 are specific for hypertension (although confirmation of these codes based on BP records would be ideal). Alternatively, in data sets with information from electronic medical records, ≥2 BP readings based on JNC-7 guidelines are sufficient for a diagnosis of hypertension.

**Presumed Diagnosis of Hypertension (Identification by Exclusion)**

Unfortunately, diagnosis codes for hypertension may not be commonly used, and few available data sets include BP readings. Therefore, patients having other diagnoses associated with the use of hypertension medications must be excluded to arrive at a population with a presumptive diagnosis of hypertension. For example, α-adrenergic antagonists (α-blockers) can also be used to treat benign prostatic hypertrophy. Patients receiving α-blockers with diagnosis codes for benign prostatic hypertrophy should be eliminated from the analysis. Similarly, patients receiving hypertension medications that are also indicated for edema, heart failure, arrhythmias, and/or angina who also have diagnosis codes for these conditions should be excluded. Exclusion of patient groups may restrict the generalizability of study results, and the remaining patients do not necessarily have hypertension (nor is it certain that the excluded patients do not), but the remaining patients are more likely to have this diagnosis and constitute a more appropriate population for evaluating hypertension outcomes.

**Comorbid Diagnoses**

BP control may be more difficult to achieve among patients with a number of comorbid conditions. For example, achieving BP control has been reported to be more difficult in patients with diabetes. In addition, controlled BP levels (as specified by JNC-7 guidelines) vary by comorbid conditions. For patients with diabetes or chronic renal disease, target BP is <130/80 mm Hg compared with <140/90 mm Hg for patients without these comorbid conditions. In addition, comorbid conditions may affect selection of hypertension medications to avoid exacerbating other conditions or causing medication interactions. Thus, determination of the proportion of patients with relevant comorbid conditions (and potentially exclusion or separate analyses of these patients) is important in evaluating the impact of hypertension therapy. Whereas these concomitant conditions by themselves may not directly affect compliance or persistence, knowing the proportion of patients with relevant comorbid conditions is crucial for comparing compliance, persistence, and outcomes among different study populations. Alternatively, differences in comorbidities can be examined and controlled for among study populations using a summary score, such as the Charlson Index or the Chronic Disease Score.

Furthermore, a number of comorbid conditions may directly affect compliance in hypertension. For example, depression has been reported to be significantly associated with noncompliance. Controlling for depression is, therefore, important in evaluating compliance with hypertension therapy.

**Geographic and Health Plan Data**

Practice patterns in the treatment of hypertension, including choice of drugs and medication additions/changes, may vary by practice setting, urban or rural location, or region within a country, as well as by showing substantial variation between countries. Practice patterns, such as medication selection, may also be influenced by patients’ insurance or health plan, including approved medications, available first-line medications, and copayments. If data on these factors are available, they should be included (and controlled for) in analyses of treatment regimens, compliance, persistence, and outcomes. In addition, geographic and health plan differences may have substantial effects on the generalizability of results. These factors must be considered in interpreting study results, particularly with respect to the generalizability of results from any one setting, region, or country.

**BP**

A limited number of data sets include electronic medical records or similar information with actual BP values. BP readings can be based on data collected in health care facilities and/or from home BP readings. When available, BP constitutes the most important short-term (ie, intermediate) clinical outcome measure in evaluating the effectiveness of hypertension therapy. However, BP readings are likely to vary by the body location (arm versus wrist measurements) and the geographic site (home versus office versus pharmacy) of BP assessments. For example, BP readings taken by medical personnel may be higher than those recorded in other environments (the so-called “white coat effect”). Analyses of BP should focus on changes in systolic and diastolic BP over the study period, as well as control, that is, time with BP below JNC-7 threshold values. Details regarding analysis of BP data are presented in the section on Outcomes (below).

**Height and Weight**

Obesity is not only a major risk factor for the development of hypertension but is also associated with treatment failure. Evaluating treatment outcomes among patients with hypertension may be confounded by obesity, because both obesity and hypertension are cardiovascular disease risk factors. In evaluating the relationship between compliance/persistence and treatment outcomes, it would be ideal to consider obesity. Unfortunately, the ICD-9 diagnosis code for obesity (278.0) is rarely used except for extreme cases, and height and weight values are not usually present, even in otherwise detailed data sets. If height and weight are present, body mass index should be calculated and used to control for the effects of obesity on hypertension outcomes. If only weight is present, it can also be used, with reference comparisons to age- and gender-based averages to identify obese patients.
Determination of Compliance and Persistence

Measurement of Compliance

In prospective studies, compliance can be measured by a variety of methods, including pill counts, blood or urine drug levels (for certain medications), patient self-report, or electronic monitoring systems, such as medication event management systems (MEMS). However, methods for assessment of compliance are limited when using retrospective data. A commonly used metric is the medication possession ratio (MPR), the ratio of total days of medication supplied (not including the last prescription) to total days in a period of time. An example illustrating calculation of MPR is presented in the Figure. Many claims databases do not provide information on days supplied for prescriptions but do include amount dispensed; to determine MPR, the number of pills dispensed and doses per day (either from the database or from standard medication references) can be used to estimate the number of days supplied.

Assessment of MPR requires patients receiving ≥2 prescriptions for the medication being assessed to have a defined time frame during which therapy was received. Calculated MPR is always >0, because the numerator (days of medication dispensed) is necessarily >0. An MPR of 1.0 indicates full (100%) compliance with therapy. MPR can be >1.0 if the number of days supplied are greater than the number of days in the period. Although this may reflect patients refilling prescriptions before the end of their medication supply or hoarding medication for later use, it is unlikely that patients will actually use hypertension drugs at greater than the prescribed frequency. Therefore, MPR should be capped at 1.0.

For patients receiving multiple concomitant hypertension medications, MPR should be calculated for each separately. The overall MPR is the average of the individual MPR values. Care should be taken in using average MPR values, however, because compliance may vary across different medications. Only 1 MPR should be calculated for a fixed-dose combination medication (ie, a single medication that contains ≥2 active ingredients).

In evaluating the impact of compliance on outcomes, MPR is often used as a dichotomous variable, with values ≥80% considered compliant. This threshold value of 80% is close to the average compliance value, 76%, reported by Cramer across several studies of hypertension medications.

Although use of this threshold makes statistical analysis easier, it is based more on custom or anecdotes rather than on pharmacological evidence; in resistant hypertension, substantially higher compliance may be required for therapy to be effective. MPR should be included as a continuous variable in regression analyses that evaluate the impact of a unit change in MPR. If used as a dependent variable in regressions, the potential nonnormal distribution of MPR must be evaluated and appropriate statistics used. These 2 types of analyses provide different information, and both should be included in studies of compliance and outcomes.

Several limitations to MPR calculations are related to the nature of retrospective databases. For example, patients may obtain the medication(s) of interest from sources not captured in the available data, such as drug samples, sharing medication with others (eg, family members), and obtaining medication from other suppliers (eg, mail order). The main limitation to MPR calculations (ie, not related to retrospective data) is the assumption that the proportion of days covered by a prescription corresponds to the proportion of days of medication used. Patients may fill prescriptions at regular intervals yet not take the medication in the manner prescribed. Nevertheless, MPR is the accepted standard for the evaluation of compliance using retrospective data, is easy to calculate, and is the most commonly used metric, allowing for comparisons among studies. Furthermore, the MPR is significantly associated with other compliance measures, drug serum levels, and clinical drug effects. MPR is the best available measure for assessing compliance to hypertension medications using retrospective data.

Treatment Discontinuation

Treatment discontinuation refers to patients stopping medication use permanently or at least with no plans to resume use. Given that a patient may subsequently restart a medication, an operational definition of treatment discontinuation requires establishing the minimum period of disuse that distinguishes this behavior from noncompliance. Treatment discontinuation has been most commonly defined as >60 days between the end of 1 dispensed medication supply and any subsequent claim for the same medication. A minimum of 60 days is generally used, because many prescriptions include 30 days of supplied medication; 60 days without therapy would, therefore, indicate missing 2 adjacent prescriptions. If the standard duration of a prescription is different than 30 days, it is recommended to use the time corresponding to 2 missed prescriptions as the minimum period for treatment discontinuation.

For this calculation, only the amount of medication dispensed in the prescription immediately preceding the 60-day period will be considered. Medication “left over” from previous prescriptions (ie, when refills are made before the end of the days supplied) should not be used in determining treatment discontinuation. Dose titration (as discussed below) is not considered a switch to a different medication and does not identify discontinuation. Given the uncertainty in the definition of treatment discontinuation, sensitivity analyses should also be performed to determine the impact of changing
the definition from 60 to 30 or 90 days (or corresponding values if the average prescription period is not 30 days).

**Treatment Persistence**
Persistence is the continued use of a medication or medications (ie, no discontinuation) for a specified period of time. It is quantified from the index date until the date of treatment discontinuation; if no discontinuation occurs during the study window, persistence is censored at the end of the available study data. Persistence is determined as a dichotomous variable for a specified period of time; for example, was a patient persistent at 6 months or at 1 year? The proportion of patients persistent at a given time and the average duration of persistence (ie, the average time from treatment initiation to discontinuation) are then calculated. The duration of persistence can be evaluated using 3 approaches that are presented in detail in Table 4.

**Medication Persistence**
Medication persistence is the time on a given medication, from initiation of therapy to the end of the study period or the end of the last supplied prescription for that medication before discontinuation of that medication.

**Regimen Persistence**
Regimen persistence is the time on a specified set of medications from initiation of therapy with that set to any change in the set of medications being received (additions or discontinuations) or the end of the study period. This metric is used to evaluate persistence with combination therapy involving ≥2 separate medications, for example, an angiotensin-converting enzyme inhibitor and a diuretic that are not a single, combined drug. This approach goes beyond medication persistence in that the period of regimen persistence ends if any part of the overall treatment regimen is changed.

**Therapy Persistence**
Therapy persistence is the time on any hypertension medications, from initiation of therapy to discontinuation of all medications or the end of the study period. This metric is similar to that for medication persistence but allows for the duration of persistence to continue for the entire period that a patient receives any hypertension medication.

Dose changes (eg, titrations) should not be considered in calculating the duration of persistence (ie, changes will not be considered either a treatment discontinuation or addition). Persistence can be studied in terms of its duration (mean, median, distribution, etc) and as a time-dependent rate (eg, proportion of patients persistent at 6 and 12 months). Duration of medication persistence should be determined separately for patients receiving monotherapy versus those receiving combination therapy.

Whereas the above definitions of persistence focus on ≥1 specific medication, persistence with a class of medications can also be assessed. For example, this would be of interest in the continued use of a class of drugs in health plans requiring switches to generic medications.

### Impact of Achieving BP Control on Measuring Compliance and Persistence

The implications of compliance and persistence differ before versus after a patient first achieves BP control. Before first achieving BP control, compliance reflects the extent to which a patient takes therapy as indicated to reach a goal (ie, controlled BP). After BP control, compliance reflects taking therapy as indicated to maintain the BP goal. Motivations for reaching versus maintaining BP control may differ, and, thus, compliance may vary before versus after achieving BP control.

The time to first achievement of BP control needs to be differentiated from duration of persistence. Preliminary results suggest that greater time on therapy before achieving BP control indicates a lack of treatment success or harder-to-control BP, whereas the duration of persistence after achieving the goal is associated with improved BP outcomes. Duration of persistence and persistence rates should, therefore, be evaluated separately before versus after achieving control if information on BP is available.

In this discussion, it is important to note that “achieving BP control” is not a permanent state; patients with hypertension will likely have increases and decreases in BP over time, going in and out of control. “Time to first achieving control” is, therefore, a somewhat artificial point in that control may not be maintained. However, because the implications for time required before first achieving BP control versus duration of persistence after achieving control are quite different, overall duration of persistence and duration of persistence after first achieving control should be considered separately if BP data are available. Thus, it is important to view compliance and persistence information in relationship to clinical data; the same compliance profile may have different meanings for patients with controlled versus elevated BP.

### TABLE 4. Classifications of Treatment Persistence

<table>
<thead>
<tr>
<th>Type of Persistence</th>
<th>Definition</th>
<th>Impact of Medication Addition on Persistence</th>
<th>Impact of Medication Switching on Persistence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication persistence</td>
<td>Time on a specific drug from initiation of therapy to end of study period or last supplied prescription</td>
<td>No impact</td>
<td>Ends period of persistence</td>
</tr>
<tr>
<td>Regimen persistence</td>
<td>Time on specified set of medications from initiation of therapy with that set to any change in the medications or end of the study period</td>
<td>Ends period of persistence</td>
<td>Ends period of persistence</td>
</tr>
<tr>
<td>Therapy persistence</td>
<td>Time on any hypertension medications from initiation of therapy to discontinuation of all medications or end of the study period</td>
<td>No impact</td>
<td>No impact</td>
</tr>
</tbody>
</table>
Consideration of Titration, Addition, and Switching

Several types of changes in medication use can be identified in retrospective analyses. Titration refers to changes in dose (either increases or decreases) prescribed by a doctor to optimally treat hypertension (further reduce BP or decrease adverse effects). Although titration may have implications for costs and clinical outcomes, it is not a change reflecting lack of compliance or persistence. Thus, measurements of compliance and persistence should not consider dose changes.

Switching refers to discontinuation of 1 medication (as defined above) with initiation of a new medication at approximately the same time. “Approximately the same time” is subject to interpretation; this can be within a specified window around the discontinuation event, based either on a fixed period of time (eg, ±1 month) or on the duration of 1 medication refill. The time period for medication switching may provide important information regarding clinical outcomes and treatment patterns that should be studied in retrospective analyses. Early switching (ie, shortly after initiation of a therapy) is likely to reflect adverse events, whereas switching after a longer period may reflect failure of reaching BP control. However, medications may also be switched if a patient develops a comorbid condition (eg, diabetes or congestive heart failure) and requires a different medication either to treat both hypertension and the new condition or to avoid contraindications with the new condition or other newly initiated medications. Therefore, switching may not always indicate a treatment failure.

Additions of new hypertension medications may also represent clinical failures (ie, inability to control BP using the current treatment regimen), although (similar to the discussion of switching, above) medications can be added to treat newly diagnosed comorbid conditions. However, additions do not affect evaluations of treatment compliance, because they do not involve changes in the use of the medication or medications being assessed. Furthermore, additions may or may not be considered failure events with respect to the determination of persistence, depending on the analysis being performed. In assessing medication persistence or therapy persistence (as described above in the Determination of Compliance and Persistence section), additions do not affect persistence, whereas the addition of new hypertension medications is viewed as discontinuation of the previous regimen in evaluating regimen persistence.

Conclusions

Clinical evidence overwhelmingly indicates that hypertension increases risks for morbidity and mortality and that hypertension therapies can decrease both. However, the available evidence also indicates that a substantial proportion of hypertensive patients are not successfully treated for their condition, and a key factor in this lack of success is diminished compliance and persistence. Compliance and persistence are preconditions for effectiveness of hypertension therapy, and the greatest potential for improvement of hypertension control lies in improving these patient behaviors.

To improve the health and quality of life of patients with hypertension, as well as to save money (because no one profits from medications that are purchased but not appropriately taken), it is crucial to further explore the relationships linking patient, medication, and health system characteristics to compliance and persistence. These results can, in turn, be used to develop new interventions to improve patient compliance and persistence. Before these relationships with compliance and persistence can be fully explored, however, there must be agreement on the types of data sources to be used and groups of patients to be included, on the types of information necessary for such analyses, and on the definitions of the compliance and persistence metrics to be calculated. Without standardization of research approaches and methods, individual studies will not provide comparable information and will not be able to be joined together as pieces of a whole.

Retrospective databases are a rich source of information on patient medication behaviors in real world settings, providing important insights regarding compliance and persistence with hypertension medications. The limitations of analyses using retrospective data largely reflect the available types of database, ie, the clinical and patient variables present for any evaluation. As more comprehensive retrospective databases become available, including electronic medical records with BP values, evaluations using databases will become more important in assessing the relationships among medication choices, patient behaviors, and clinical outcomes. In this document, we have recommended standards and methods for evaluating hypertension compliance and persistence using retrospective data. We hope that these recommendations will help to remove obstacles present in this field and to provide a framework for studies that can be easily compared.

A key element to consider in any retrospective analysis (or, more broadly, any analysis regardless of type of data) is the eventual audience (the groups or organizations that will “use” the study results). Analyses of hypertension compliance and persistence need to provide information relevant to the intended users. As such, the types of databases to be used, patients to be included, and outcomes to be assessed must be selected in light of the users’ needs. For example, some users may simply need data on compliance and persistence with hypertension medications, whereas others will require more detailed information, including treatment-related adverse effects and clinical and economic outcomes. The use of appropriate methods for analysis, as well as suitable data sources, will be crucial in addressing the information needs of the intended audience. The recommendations presented in this document will help in meeting these information needs and ensuring that disparate studies provide comparable results.

Although we have focused on recommendations for retrospective studies, other forms of analysis are also important in evaluating the link between compliance/persistence and outcomes in hypertension. Discussion of other types of studies is beyond our scope, but many of our recommendations apply to prospective evaluations as well. Furthermore, retrospective studies do not exist in isolation. For example, compliance and persistence data from retrospective analyses are often used in models to understand the impacts of specific medications on
resource use and costs; these results may then be used for formulary committee dossiers, treatment guidelines, and decisions by payers and health authorities. Retrospective studies are also often used for hypothesis testing to develop the questions to be addressed in specific prospective evaluations. Thus, compliance and persistence data from retrospective analyses form the foundation of a broader understanding of the factors affecting clinical, quality-of-life, and economic outcomes among individuals with hypertension. As such, use of good research practices and appropriate methods for retrospective analyses will have broader impacts on health care systems overall.

**Perspectives**

Given the clear evidence for effectiveness of hypertension therapy, the paucity of data linking treatment compliance and persistence with improved BP outcomes suggests that these behaviors are often not appropriately assessed or analyzed. The recommendations presented in this tutorial describe standardized approaches for identifying data sources, defining patient cohorts, assessing the information needed to perform a study, and evaluating compliance and persistence with hypertension therapy. This will allow researchers to assess the impact of compliance and persistence on BP outcomes and, in turn, to evaluate the clinical and health system impacts of interventions designed to improve these medication behaviors. In this era of evidence-based medicine, quantifying compliance and persistence with hypertension therapy will provide additional information to clinicians and other health care decision makers on the full range of factors impacting treatment effectiveness, including patients beliefs, attitudes, and behaviors.

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**References**


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