Hypertension

Meta-Analysis
Impact of Drug Class on Adherence to Antihypertensives

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Background—Observational studies suggest that there are differences in adherence to antihypertensive medications in different classes. Our objective was to quantify the association between antihypertensive drug class and adherence in clinical settings.

Methods and Results—Studies were identified through a systematic search of English-language articles published from the inception of computerized databases until February 1, 2009. Studies were included if they measured adherence to antihypertensives using medication refill data and contained sufficient data to calculate a measure of relative risk of adherence and its variance. An inverse-variance-weighted random-effects model was used to pool results. Hazard ratios (HRs) and odds ratios were pooled separately, and HRs were selected as the primary outcome. Seventeen studies met inclusion criteria. The pooled mean adherence by drug class ranged from 28% for β-blockers to 65% for angiotensin II receptor blockers. There was better adherence to angiotensin II receptor blockers compared with angiotensin-converting enzyme inhibitors (HR, 1.33; 95% confidence interval, 1.13 to 1.57), calcium channel blockers (HR, 1.57; 95% confidence interval, 1.38 to 1.79), diuretics (HR, 1.95; 95% confidence interval, 1.73 to 2.20), and β-blockers (HR, 2.09; 95% confidence interval, 1.14 to 3.85). Conversely, there was lower adherence to diuretics compared with the other drug classes. The same pattern was present when studies that used odds ratios were pooled. After publication bias was accounted for, there were no longer significant differences in adherence between angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors or between diuretics and β-blockers.

Conclusion—in clinical settings, there are important differences in adherence to antihypertensives in separate classes, with lowest adherence to diuretics and β-blockers and highest adherence to angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors. However, adherence was suboptimal regardless of drug class. (Circulation. 2011;123:1611-1621.)

Key Words: hypertension ■ medication adherence ■ meta-analysis

Hypertension is the most common chronic illness in developed countries and one of the most important risk factors for cardiovascular disease. Numerous studies have shown that blood pressure lowering is associated with major reductions in coronary events, strokes, and mortality. Although counseling about lifestyle factors plays a role, prescribing antihypertensive medications remains the cornerstone of the medical management of hypertension.

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Clinical practice guidelines such as the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Hypertension have been developed to assist clinicians in their selection of antihypertensive medications. These guidelines rely heavily on data from clinical trials to inform their preferences for antihypertensive medications. However, as a result of selection bias, run-in periods, and behavior reinforcement through close follow-up, adherence to medication in clinical trial settings may not be representative of adherence in real-world settings. For example, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the level of adherence to treatment at 1 year ranged from 83% to 88%, depending on drug class. In observational studies, adherence to antihypertensive medications is typically much lower. Accordingly, clinical trials such as ALLHAT may underestimate the impact of differences in adherence to medications from separate drug classes in clinical settings.

The literature describing the association between antihypertensive drug class and adherence is characterized by a wide variety of patient populations, drug class comparisons,
and definitions of adherence. This heterogeneity has made it difficult to draw conclusions about the clinical relevance of differences in adherence according to drug class. Quantifying the overall impact of drug class on adherence in observational settings would provide important evidence to guide the selection of blood pressure medications and to guide adherence monitoring. Accordingly, we performed a meta-analysis to determine the impact of antihypertensive drug class on adherence to blood pressure medications.

Methods

Data Sources and Searching

This study was performed as part of a larger systematic review of predictors of adherence to oral cardiovascular and diabetic medications. The research methodology was done in accordance with Meta-Analysis of Observational Studies in Epidemiology guidelines.9 With the assistance of a medical librarian (L.F.), potentially relevant articles were identified by searching publicly available computerized databases. The search included all articles and abstracts (including unpublished doctoral theses) referenced from database inception to February 1, 2009, in MEDLINE, the Database of Abstracts of Reviews of Effects, the National Health Service Abstracts (including unpublished doctoral theses) referenced from computerized databases. The search included all articles and abstracts (including unpublished doctoral theses) referenced from database inception to February 1, 2009, in MEDLINE, the Database of Abstracts of Reviews of Effects, the National Health Service Economic and Evaluation Database, the Health Technology Assessment Database, EMBASE, and PsyCINFO. All relevant subject heading and free text terms for adherence or compliance and for both the generic class of drug (eg, β-blocker [BB] and angiotensin-converting enzyme inhibitor [ACEI]) and the individual names of antihypertensive medications, generic and proprietary, were included (Appendix I in the online-only Data Supplement). Because of the large volume of literature on this topic, a set of methodological filters was applied to the search strategies of the larger databases (MEDLINE, EMBASE, and PsyCINFO). Follow-up searches were performed by searching bibliographies from selected articles by hand.

Study Selection

Articles were eligible for inclusion if they were published in English and included community-dwelling patients ≥18 years of age. Eligible study designs included observational cohorts in which adherence to antihypertensive medication was evaluated as an outcome. To reduce heterogeneity when the studies were pooled, studies were eligible only if they measured adherence using medication refill data. Articles also had to include data that compared adherence between at least 2 distinct antihypertensive drug classes, and had to report sufficient data to calculate a measure of relative risk of adherence and its variance.

A number of sociodemographic characteristics, medical and psychological conditions, and regimen complexity qualities have been shown to influence adherence.10–11 Accordingly, studies were excluded if they did not consider at least 1 potentially confounding characteristic in their analyses of the association between drug class and adherence. Studies in which adherence was measured by determining whether patients were taking a medication at a single time point were also excluded, because this was not equivalent to studying adherence with a regimen over time. For the remaining studies, we assigned a quality rating using a checklist adapted from the recommendations of the International Society of Pharmacoeconomics and Outcomes Research (Appendix II in the online-only Data Supplement).12,13 Two investigators (D.M., I.K.) independently reviewed all citations identified through the literature search using a predefined protocol. Articles that clearly did not meet inclusion criteria were excluded at the title and abstract level. The remaining articles were selected for full text review. When limited information was available from the abstract, full text was always obtained. Included articles underwent a quality assessment by 2 investigators (Z.S., I.K.). Disagreements regarding the selection and quality assessment of articles were resolved through discussion, and full consensus was achieved at each stage of review.

Data Synthesis and Analysis

Two pairs of studies15–18 included overlapping data; hence, 2 studies were excluded from quantitative analysis.15–17 The remaining studies were grouped for pooling according to comparisons of adherence between pairs of drug classes. Data were then subgrouped according to whether the measure of relative risk was an odds ratio or HR. The pooled HR of adherence was selected as the primary outcome because this was the most frequently used measure of adherence in the pooled studies, and because the HR accounts for censoring and is thus preferred as a measure of relative risk with prospective data. Angiotensin II receptor blockers and diuretics were selected as the generic antihypertensive classes, and had to report sufficient data to allow the calculation of relative risks for each drug class.

Two investigators (Z.S., I.K.) independently extracted data from selected studies using a standardized form. Information was collected regarding dates and sizes of the studies, types of patients enrolled, duration of follow-up, types of drug classes assessed, whether patients were concurrently taking antihypertensive medications from other drug classes, the proportion initiating angiotensin II receptor blockers (ARBs), and whether the study had any pharmaceutical industry affiliation. Pharmaceutical affiliation was ascribed if the study received funding from a pharmaceutical company or if the study author was employed by or served as a consultant for the industry. Adherence data pertaining to combination antihypertensive pills were not extracted.

Investigators also recorded the method used to define adherence, the mean adherence according to drug class, the measure of the relative risk of adherence between pairs of drug classes, and the types of covariates included in adjusted analyses. In accordance with the International Society of Pharmacoeconomics and Outcomes Research guidelines,14 we defined adherence as an umbrella term that encompasses 2 related categories of pill-taking behavior: compliance and persistence. Adherence was categorized as compliance if it measured the proportion of days covered with medication, calculated as the sum of the days’ supply for all prescriptions filled during the study time period divided by the total number of days in this time period. Individuals were then defined as compliant or noncompliant using a threshold of 80% for proportion of days covered. Adherence was categorized as persistence if it referred to either a continuous measure of the number of days on a given antihypertensive from initiation of therapy to the end of the last supplied prescription in the study period before a significant gap in coverage with the medication, or a dichotomous variable in which patients were categorized as persistent or nonpersistent depending on whether they had any significant gaps in coverage during the study period. Persistence studies were subgrouped according to whether they defined persistence as medication persistence (time to discontinuation of a given medication) or therapy persistence (time to discontinuation of all antihypertensive medication).15–17 Dichotomous measures of adherence were used to calculate odds ratios for adherence between 2 drug classes using logistic regression. Continuous measures of adherence were used to calculate hazard ratios (HRs) using Cox proportional hazards regression.

Data Extraction

Two investigators (Z.S., I.K.) independently extracted data from selected studies using a standardized form. Information was collected regarding dates and sizes of the studies, types of patients enrolled, duration of follow-up, types of drug classes assessed, whether patients were concurrently taking antihypertensive medications from other drug classes, the proportion initiating angiotensin II receptor blockers (ARBs), and whether the study had any pharmaceutical industry affiliation. Pharmaceutical affiliation was ascribed if the study received funding from a pharmaceutical company or if the study author was employed by or served as a consultant for the industry. Adherence data pertaining to combination antihypertensive pills were not extracted.

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class across studies that measured adherence as persistence. We weighted our calculations according to person-months of exposure.

**Results**

**Qualitative Analysis (n=17)**
The comprehensive search yielded 115 unique articles related to predictors of adherence to antihypertensive medications (Figure 1). Seventeen articles met the inclusion criteria15–18,20–32 (Table). Five studies were rated “excellent” and satisfied all the requirements on the quality checklist; 12 studies were rated “good” and were missing 1 or 2 items on the checklist. Included articles assessed adherence to antihypertensive medications between 1989 and 2004 for 935,920 patients. The studies measured adherence using medication refill data from either insurance claims or pharmacy refills in closed pharmacy systems in North American and Europe. Thirteen articles defined adherence as persistence (5 medication persistence, 8 therapy persistence), and 4 articles defined adherence as compliance. Angiotensin II receptor blockers were the least likely drug class to be prescribed, with rates from 2% to 23%.

Articles had large differences in their selection of covariates for adjusted analyses. Covariates included demographics (age, race, sex, income, ethnicity), burden of disease (comorbidities), complexity of medication regimen (number of medications, frequency of dosing), health system barriers (insurance coverage, cost of care), healthcare use (numbers of hospitalizations and physician visits), and prescriber characteristics (type of physician).

Two articles provided data on overall compliance according to proportion of days covered.28,32 In the study by Zhang et al,32 53% were compliant to antihypertensives (either an ACEI or ARB), and in the study by Siegel et al,28 78% to 84% were compliant. The mean overall persistence with antihypertensives, available from 12 studies, ranged from 35% to 84%.

With respect to relative adherence, with 1 exception (Zhang et al),32 there was better adherence (P<0.05) to ARBs compared with other drug classes studied (ACEI, calcium channel blockers [CCBs], BB, diuretics), regardless of adherence definition (Figure 2). Conversely, with 2 exceptions (van Wijk et al18 in Canada, BB comparison; Erkens et al,23 CCB comparison), there was lower adherence to diuretics compared with other drug classes (P<0.05; Figure 3).

**Quantitative Analysis (n=15)**
The pooled mean age of patients was 61.7 years, and 53.1% were women. The pooled mean person-months of adherence observation across studies was 12.3 months. With HR as the primary measure of relative adherence, there was an increased risk of adherence to ARBs compared with ACEIs (HR, 1.33; 95% confidence interval [CI], 1.13 to 1.57), CCBs (HR, 1.57; 95% CI, 1.38 to 1.79), BBs (HR, 2.09; 95% CI, 1.14 to 3.85), and diuretics (HR,
Table. Summary of Included Studies of Association of Antihypertensive Drug Class and Adherence

<table>
<thead>
<tr>
<th>No.</th>
<th>Reference</th>
<th>Country</th>
<th>Drug Company</th>
<th>Years Enrolled</th>
<th>Patients, n</th>
<th>Drug Classes Evaluated</th>
<th>Population</th>
<th>Percent Initiating ARB</th>
<th>Period Observed</th>
<th>Adherence Definition</th>
<th>Type of Adherence Measure</th>
<th>Mean Adherence Rate, %</th>
<th>Covariates</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bloom et al</td>
<td>United States</td>
<td>Yes</td>
<td>1995–1996</td>
<td>21723</td>
<td>Losartan, ACEI, CCB, BB, diuretic</td>
<td>Initiating a first medication for treatment of HTN</td>
<td>2.6</td>
<td>12 mo</td>
<td>Retired first prescription on or within 3 mo of the 1-y anniversary of first prescription</td>
<td>Medication persistence*</td>
<td>64 ARB, 58 ACE, 50 CCB, 43 BB, 38 thiazide</td>
<td>1, 2, 9</td>
<td>Good</td>
</tr>
<tr>
<td>2</td>
<td>Caro et al</td>
<td>Canada</td>
<td>Yes</td>
<td>1989–1994</td>
<td>22918</td>
<td>ACEI, CCB, BB, diuretic</td>
<td>Initiating a first medication for treatment of HTN</td>
<td>0</td>
<td>12 mo</td>
<td>Last prescription covered period until the end of observation period</td>
<td>Therapy persistence†</td>
<td>89 ACEI, 86 CCB, 85 BB, 80 diuretic, 84 overall (at 6 mo)</td>
<td>1, 2, 9, 10</td>
<td>Good</td>
</tr>
<tr>
<td>3</td>
<td>Esposti et al</td>
<td>Italy</td>
<td>Yes</td>
<td>1997</td>
<td>16783</td>
<td>Losartan, ACEI, CCB, BB, diuretic</td>
<td>Initiating a first medication for treatment of HTN</td>
<td>1.9</td>
<td>12 mo</td>
<td>Days elapsed between first and last prescriptions</td>
<td>Therapy persistence</td>
<td>58 ARB, 40 ACEI, 31 CCB, 38 BB, 30 diuretic, 35 overall (&gt;273 d elapsing between first and last prescriptions)</td>
<td>1, 2, 6, 7, 10</td>
<td>Good</td>
</tr>
<tr>
<td>4</td>
<td>Erkens et al</td>
<td>Netherlands</td>
<td>Yes</td>
<td>1997–2001</td>
<td>2243</td>
<td>ARB, ACEI, CCB, BB, diuretic</td>
<td>Initiating a first medication for treatment of HTN</td>
<td>19.9</td>
<td>12 mo</td>
<td>Days elapsed between first and last prescriptions and additional prescription within 3 mo after 1 y</td>
<td>Therapy persistence</td>
<td>62 ARB, 60 ACE, 35 CCB, 35% BB, 33 diuretic, 44 overall</td>
<td>1, 8, 10</td>
<td>Good</td>
</tr>
<tr>
<td>5</td>
<td>Elliott et al</td>
<td>United States</td>
<td>Yes</td>
<td>2001–2002</td>
<td>60685</td>
<td>Valsartan, lisinopril, amlodipine, diuretic</td>
<td>Initiating a new medication for HTN; eligible if continuing prior HTN medication</td>
<td>15.3</td>
<td>12 mo</td>
<td>Days until lapse in therapy for &gt;60 d</td>
<td>Medication persistence</td>
<td>69 Valsartan, 65 lisinopril, 60 amlodipine, 56 HCTZ, 62 overall; no lapse in therapy for &gt;60 d</td>
<td>1, 2, 7, 8, 15</td>
<td>Good</td>
</tr>
<tr>
<td>6</td>
<td>Mazzaglia et al</td>
<td>Italy</td>
<td>Yes, minor</td>
<td>2000–2001</td>
<td>13303</td>
<td>ARB, ACEI, CCB, BB, diuretic</td>
<td>Initiating a first medication for treatment of HTN other than combination pills</td>
<td>10.4</td>
<td>12 mo</td>
<td>Days until lapse in therapy for &gt;60 d</td>
<td>Therapy persistence</td>
<td>61 ARB, 63 ACEI, 64 CCB, 58 BB, 50 diuretic, 47 overall (estimated from bar graph); no lapse in therapy for &gt;60 d</td>
<td>1, 2, 6, 7, 14, 16</td>
<td>Excellent</td>
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<tr>
<td>7</td>
<td>Monane et al</td>
<td>United States</td>
<td>No</td>
<td>1982–1988</td>
<td>8643</td>
<td>ACEI, CCB, diuretic</td>
<td>Initiating a first medication for treatment of HTN; seniors (65 y old) receiving Medicaid</td>
<td>0</td>
<td>12 mo</td>
<td>PDC ≥80%</td>
<td>Compliance</td>
<td>20 Overall</td>
<td>1, 2, 3, 15</td>
<td>Excellent</td>
</tr>
<tr>
<td>8</td>
<td>Perrault et al</td>
<td>Canada</td>
<td>No</td>
<td>1998–2000</td>
<td>21011</td>
<td>ARB, ACEI, CCB, BB, diuretic, combined</td>
<td>Initiating a first medication for treatment of HTN</td>
<td>13.0</td>
<td>12 mo</td>
<td>No lapse in therapy for ≥60 d</td>
<td>Therapy persistence</td>
<td>73 ARB, 71 ACEI, 68 CCB, 61 BB, 61 diuretic, 66 combination, 67 overall</td>
<td>1, 2, 4, 5, 8, 9, 10</td>
<td>Excellent</td>
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<td>9</td>
<td>Siegel et al</td>
<td>United States</td>
<td>No</td>
<td>2002–2003</td>
<td>40492</td>
<td>ARB, ACEI, CCB, diuretic</td>
<td>Continuing or initiating a single medication for HTN; AB, diuretic eligible if continuing prior HTN medication; veterans only; at least 1 refill for drug class of interest during study period</td>
<td>8.4</td>
<td>18 mo</td>
<td>PDC ≥80%</td>
<td>Compliance</td>
<td>84 ARB, 81 ACEI, 83 CCB, 80 BB, 79 AB, 78 diuretic (includes patients on multiple HTN medications)</td>
<td>1, 2, 3, 6, 9</td>
<td>Good</td>
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<tr>
<td>10</td>
<td>Taira et al</td>
<td>United States</td>
<td>No</td>
<td>1999–2003</td>
<td>28395</td>
<td>ARB, ACEI, CCB, BB, diuretic</td>
<td>Initiating a first medication for treatment of HTN</td>
<td>Not reported</td>
<td>3 y</td>
<td>PDC ≥80%</td>
<td>Compliance</td>
<td>Not reported</td>
<td>1, 2, 5, 6, 13</td>
<td>Good</td>
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</table>

(Continued)
<table>
<thead>
<tr>
<th>No.</th>
<th>Reference</th>
<th>Country</th>
<th>Drug Company Affiliation</th>
<th>Years</th>
<th>Patients, n</th>
<th>Drug Classes Evaluated</th>
<th>Population</th>
<th>Percent Initiating ARB</th>
<th>Period Observed</th>
<th>Adherence Definition</th>
<th>Type of Adherence Measure</th>
<th>Mean Adherence Rate, %</th>
<th>Covariates</th>
<th>Quality Rating</th>
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<tr>
<td>11</td>
<td>Taira et al[16]</td>
<td>United States</td>
<td>Yes</td>
<td>1999–2004</td>
<td>114,232</td>
<td>All drug classes</td>
<td>Continuing or initiating medication treatment for HTN; eligible if continuing prior HTN medication</td>
<td>Not reported</td>
<td>12 mo</td>
<td>PDC ≥80%</td>
<td>Compliance</td>
<td>Not reported</td>
<td>1, 2, 3, 6, 11, 12</td>
<td>Good</td>
</tr>
<tr>
<td>12</td>
<td>Van Wijk et al[17*]</td>
<td>Netherlands</td>
<td>No</td>
<td>1992–2002</td>
<td>2325</td>
<td>ARB, CCB, BB, AB, diuretic</td>
<td>Initiating a first medication for treatment of HTN; no other indications for HTN medication (eg, CVD, migraine); at least 1 refill for drug class of interest during study period</td>
<td>Not reported</td>
<td>10 y</td>
<td>Refilled first prescription at least 2 times per year</td>
<td>Medication persistence</td>
<td>61 Overall (includes patients who discontinued and restarted during 10–y period)</td>
<td>1, 2, 12, 13</td>
<td>Good</td>
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<tr>
<td>13</td>
<td>Esposti et al[29]</td>
<td>Italy</td>
<td>Yes</td>
<td>2000</td>
<td>14,062</td>
<td>ARB, ACEI, CCB, BB, diuretic</td>
<td>Initiating a first medication for treatment of HTN</td>
<td>6.9</td>
<td>12 mo</td>
<td>Days elapsed between first and last prescriptions</td>
<td>Therapy persistence</td>
<td>55 ARB, 43 ACEI, 35 CCB, 43 BB, 33 diuretic, 40 overall; &gt; 273 d elapsed between first and last prescriptions</td>
<td>1, 6, 7, 10</td>
<td>Good</td>
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<tr>
<td>14</td>
<td>Corrao et al[30]</td>
<td>Italy</td>
<td>No</td>
<td>1999–2002</td>
<td>445,356</td>
<td>All drug classes</td>
<td>Initiating a first medication for treatment of HTN; at least 1 refill for drug class of interest during study period</td>
<td>9</td>
<td>12 mo</td>
<td>Days until lapse in therapy for ≥60 d</td>
<td>Therapy persistence</td>
<td>59 Overall; no lapse in therapy for ≥60 d</td>
<td>1, 2, 8, 15</td>
<td>Excellent</td>
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<td>15</td>
<td>Hoer et al[31]</td>
<td>Germany</td>
<td>Yes</td>
<td>2000–2003</td>
<td>62,754</td>
<td>ARB, ACEI, CCB, BB, diuretic</td>
<td>Initiating a first medication for treatment of HTN other than combination pills; no recent CVD related hospitalization; at least 1 refill for drug class of interest during study period</td>
<td>5.5</td>
<td>12 mo</td>
<td>Days until lapse in therapy for ≥60 d</td>
<td>Medication persistence</td>
<td>53 ARB, 35 ACEI, 34 CCB, 14 BB, 26 diuretic; no lapse in therapy for ≥60 d</td>
<td>1, 2</td>
<td>Good</td>
</tr>
<tr>
<td>16</td>
<td>Van Wijk et al[18]</td>
<td>US, Canada, and Netherlands</td>
<td>No</td>
<td>1998–2004</td>
<td>9664 US, 25,377 Canada, 24,603 Netherlands</td>
<td>ARB, ACEI, CCB, BB</td>
<td>Initiating a first medication for treatment of HTN; seniors (≥65 y old)</td>
<td>9.9 US, 1.6 Canada, 7.1 Netherlands</td>
<td>12 mo</td>
<td>No lapse in therapy for ≥180 d</td>
<td>Therapy persistence</td>
<td>77 US, 77 Canada, 76 Netherlands</td>
<td>1, 2, 3, 4, 6, 9, 10</td>
<td>Good</td>
</tr>
<tr>
<td>17</td>
<td>Zhang et al[32]</td>
<td>US</td>
<td>No</td>
<td>2004</td>
<td>1351</td>
<td>ARB, ACEI</td>
<td>Initiating ARB or ACEI; eligible if continuing prior HTN medication</td>
<td>22.8</td>
<td>6 mo</td>
<td>POC ≥80%</td>
<td>Compliance</td>
<td>53 Overall</td>
<td>1, 2, 3, 6, 8, 9, 10, 11</td>
<td>Excellent</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; BB, b-blocker; HTN, hypertension; ARB, angiotensin receptor blocker; HCTZ, hydrochlorothiazide; AB, a-blocker; CVD, cardiovascular disease; and PDC, proportion of days covered. Covariates: (1) age, (2) sex, (3) race/ethnicity, (4) income or receipt of social assistance, (5) residence, (6) comorbidity types, (7) comorbidity burden, (8) treatment with medication classes other than antihypertensives, (9) medication regimen characteristics (number of medications, frequency of dosing, number of pills per day), (10) healthcare use (prior hospitalizations, physician visits, use of other services), (11) out-of-pocket medication costs, (12) type of health insurance, (13) physician characteristics, (14) blood pressure at baseline, (15) year of first prescription, and (16) family history of comorbidities.

*Medication persistence means that patients were considered persistent if they continued the initial prescribed drug class but not if they switched, combined a medication from another drug class, or discontinued all antihypertensive medication therapy.

†Therapy persistence means that patients were considered persistent if they remained on any hypertension medications from the time of treatment initiation, which could include continuing the initially prescribed drug class, combining with another drug class, or switching to a different drug class without a lapse in treatment.

‡Not included in pooled analysis because of overlapping data in other study.
In contrast, there was a lower risk of adherence to diuretics compared with all the other drug classes (Figure 3). As a secondary analysis, 4 studies measured the relative risk of adherence using odds ratios. The pattern of relative adherence remained the same when the odds ratio was used as the measure of relative adherence, with highest adherence to ARBs and lowest to diuretics and BBs (Figures 2 and 3).
Data were available for pooled estimates of adherence for individual drug classes from 9 studies, although 2 studies contained data for only 4 of the 5 drug classes, which introduced some between-study bias. The mean persistence to medication followed the expected pattern, with highest mean persistence to ARBs at 64.9% (95% CI, 64.3 to 65.6) and ACEIs at 57.6% (95% CI, 57.2 to 57.9), intermediate persistence to CCBs at 52.0% (95% CI, 51.6 to 52.5), and lowest persistence to BBs at 28.4% (95% CI, 28.1 to 28.8) and diuretics at 51.0% (95% CI, 51.4 to 51.8).

Overall, other than the comparison between ACEIs and ARBs, there was significant heterogeneity when data were
Figure 3. Adherence to diuretics compared with other antihypertensive drug classes: meta-analysis results. Hazard ratios and odds ratios with 95% confidence intervals (CIs) on a logarithmic scale for individual or pooled study data for each pairwise comparison for relative risk of adherence between pairs of classes of blood pressure medication. Black boxes indicates studies in which adherence is measured as persistence; white boxes, studies in which adherence is measured as compliance. Adjustments: (1) age, (2) sex, (3) race/ethnicity, (4) income or receipt of social assistance, (5) residence, (6) comorbidity types, (7) comorbidity burden, (8) treatment with medication classes other than antihypertensives, (9) medication regimen characteristics (number of medications, frequency of dosing, number of pills per day), (10) healthcare use (prior hospitalizations, physician visits, use of other services), (11) out-of-pocket medication costs, (12) type of health insurance, (13) physician characteristics, (14) blood pressure at baseline, (15) year of first prescription, and (16) family history of comorbidities. ACEI indicates angiotensin-converting enzyme inhibitor; CCB, calcium-channel blocker; and BB, β-blocker.
pooled ($i^2$ statistic, 91.7% to 98.0%). This supported the use of the random-effects model to estimate the relative risk of adherence between pairs of drug classes. Given this substantial heterogeneity, we performed subgroup analyses for our primary outcome to assess the impact of different definitions of adherence, study size, quality, location, inclusion criteria, and pharmaceutical affiliation on the estimates of the relative risk of adherence by drug class. All $i^2$ values were either reduced or increased by 1% in subgroup analyses.

Subgroup analyses supported the robustness of the overall conclusions. First, we tested the impact of defining adherence as medication persistence or as therapy persistence. The definition of adherence did not change the overall pattern, with higher adherence to ARBs compared with other drugs regardless of definition; however, the difference between ARBs and ACEIs did not remain significant when we restricted the studies to those measuring adherence as therapy persistence. Similarly, subgroup analyses involving study size, location, and quality made no qualitative difference on the pattern of adherence, with higher adherence to ARBs compared with other drugs and lower adherence to diuretics compared with all other drugs, although differences between diuretics and BBs were not always statistically significant. Thirteen studies restricted their inclusion of patients to those who were initiating a first medication for hypertension and were not concurrently prescribed any other antihypertensives. There were no significant differences in the relationship between adherence and drug class when the meta-analysis was limited to these studies. Sufficient studies were available for testing the impact of pharmaceutical affiliation on relative adherence in 2 instances. The relative benefit of adherence to ARBs versus ACEIs was more pronounced ($P=0.006$) in pharmaceutical-affiliated studies (pooled HR, 1.41; 95% CI, 1.17 to 1.70; 4 pooled studies) compared with non-pharmaceutical-affiliated studies (HR, 1.09; 95% CI, 1.06 to 1.11; 1 study). There was no significant impact of pharmaceutical affiliation on the estimate of relative adherence between ARBs and diuretics.

Publication bias affected the estimate of relative adherence according to HR in 2 instances. There were no longer significant differences in adherence between ARBs and ACEIs (HR, 1.10; 95% CI, 0.94 to 1.30) or between BBs and diuretics (HR, 1.13; 95% CI, 0.89 to 1.44) after accounting for publication bias.

**Discussion**

We found that there was a significant relationship between adherence to antihypertensive medication and drug class. Compared with patients prescribed diuretics and BBs, the drug classes associated with the lowest adherence, patients prescribed ARBs were approximately twice as likely to have good adherence. Overall, ACEIs appeared to have the second-best level of adherence, followed by CCBs, although insufficient data were available for definitive ranking of pairwise comparisons, and publication bias may have accounted for differences between ARBs and ACEIs.

There was a remarkable degree of consistency in the pattern of our results showing superior adherence to ARBs and ACEIs and inferior adherence to diuretics and BBs. No single study dominated any of the pooled estimates, and there was no substantial difference in the pattern regardless of the adherence definition or the size, quality, and location of the study.

There are several possible reasons for these differences. Each of the drug classes is associated with distinct side

<table>
<thead>
<tr>
<th>Study</th>
<th>Estimate (95% CI)</th>
<th>Weight Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Wijk-Canada</td>
<td>1.18 (1.06, 1.28)</td>
<td>95%</td>
</tr>
<tr>
<td>Van Wijk-Holland</td>
<td>1.30 (1.19, 1.41)</td>
<td>95%</td>
</tr>
<tr>
<td>Mazzaglia</td>
<td>1.79 (1.67, 1.92)</td>
<td>95%</td>
</tr>
<tr>
<td>Van Wijk-US</td>
<td>1.85 (1.61, 2.13)</td>
<td>95%</td>
</tr>
<tr>
<td>Total (I-squared = 95.6%, p &lt; 0.001)</td>
<td>1.50 (1.20, 1.87)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

| Odds ratio        |                   |                    |
| Erkens            | 1.10 (0.80, 1.40) | 12.81              |
| Caro              | 1.51 (1.36, 1.69) | 22.27              |
| Siegel            | 1.55 (1.35, 1.77) | 20.75              |
| Monane            | 1.70 (1.50, 2.10) | 18.82              |
| Taira             | 1.85 (1.79, 1.90) | 25.35              |
| Total (I-squared = 86.9%, p < 0.001) | 1.57 (1.36, 1.81) | 100.00             |
effects. Diuretics, for example, can cause urinary frequency, erectile dysfunction, fatigue, and muscle cramps. They can also produce metabolic and electrolyte abnormalities that may lead physicians to discontinue them.

Another possible explanation for the differences in adherence by drug class may be variation in provider and patient beliefs about medications. Perceived benefit of treatment is a core component of several health behavior models and has been associated with adherence in some studies of cardiovascular medications. Prior studies have shown differences in physician perceptions of the effectiveness and tolerability of antihypertensive medication in separate classes. Future studies might assess whether these differences mediate the relationship between adherence and drug class.

The higher rate of adherence to ARBs compared with diuretics suggests that drug cost plays a relatively minor role in antihypertensive adherence. It is possible that cost plays a more significant role in underinsured populations in which medication users are responsible for a significant portion of prescription costs; no articles were restricted to populations without prescription insurance or with low socioeconomic status.

There are several limitations to our conclusions. First, ARBs were prescribed at lower rates than are typical currently in developed countries. This may have biased the results comparing ARBs and other drug classes. There may have been factors related to the selection of patients who are more adherent, so that adherence to ARBs may be more related to patient selection factors than to the properties of the drug class itself. Until this is assessed, it is premature to recommend ARBs as first-line medications for clinicians interested in minimizing adherence problems. Second, these findings may not be generalizable to patients who are already started on ≥1 antihypertensive medications. In practice, a growing number of patients are on multiple blood pressure medications, and some guidelines even recommend starting with combinations of drug classes for patients with blood pressure markedly above goal. Nevertheless, in our 5 studies that considered this question, the pattern of adherence between drug classes was the same. Third, these analyses involved multiple statistical tests; thus, the nominal type I error rate of 5% must be interpreted with caution. Fourth, there was significant heterogeneity when data were pooled. Still, the pattern of relative adherence remained the same in subgroup analyses. Another limitation is that we excluded articles that assessed adherence by drug class but did not report adjusted analyses of relative risks. A qualitative review of these articles was consistent with the pattern of adherence found in our meta-analysis. Finally, we did not have resources to review non–English-language publications or to contact authors for unpublished data. Of note, 1 study of Korean patients published after we completed our systematic search was also consistent with our findings, showing highest adherence to ACEIs and ARBs and lowest adherence to diuretics.

Implications

Although rates of blood pressure control are improving in the United States, more than half of hypertensive Americans continue to have blood pressure above recommended levels, and poor adherence to antihypertensives remains an important cause of poor blood pressure control. Lack of adherence to antihypertensive treatment has been associated with complications, such as increased cardiovascular events and healthcare costs. Our findings remind us that it is important for clinicians to pay attention to adherence regardless of antihypertensive drug class because rates of adherence were suboptimal for all drug classes. Clinicians should pay special attention to adherence in patients who are prescribed diuretics and BBs. Incorporating objective data from pharmacy refill claims or other sources may assist clinicians with assessing medication adherence and with optimizing their antihypertensive prescribing decisions. Clinical trials that simulate real-world settings as much as possible should be pursued to assess whether differences in adherence by drug class are associated with differences in blood pressure control and related clinical outcomes.

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Disclosures

None.

References

determine the impact of antihypertensive drug class on adherence to blood pressure medications. We found that there was
descriptiveness determinants. This heterogeneity has made it difficult to make firm conclusions about
describing the association between drug class and adherence is characterized by a wide variety of patient populations, drug
that there may be important differences in adherence to antihypertensives in distinct drug classes. Yet, the literature
adherence in patients who are prescribed diuretics and
for definitive rankings. Our findings demonstrate that it is important for clinicians to pay attention to adherence regardless
to have the second-best level of adherence, followed by calcium channel blockers, although insufficient data were available
for definitive rankings. Our findings demonstrate that it is important for clinicians to pay attention to adherence regardless of
drug class because adherence was suboptimal for all drug classes and that clinicians should pay special attention to
adherence in patients who are prescribed diuretics and β-blockers.

## CLINICAL PERSPECTIVE

More than half of US individuals with hypertension continue to have blood pressure above recommended levels, and poor adherence to antihypertensives remains an important cause of poor blood pressure control. Observational studies suggest that there may be important differences in adherence to antihypertensives in distinct drug classes. Yet, the literature describing the association between drug class and adherence is characterized by a wide variety of patient populations, drug class comparisons, and definitions of adherence. This heterogeneity has made it difficult to make firm conclusions about the clinical relevance of differences in adherence according to drug class. Accordingly, we performed a meta-analysis to determine the impact of antihypertensive drug class on adherence to blood pressure medications. We found that there was a significant relationship between adherence and antihypertensive drug class. Compared with patients prescribed diuretics and β-blockers, the drug classes associated with the lowest adherence, patients prescribed angiotensin II receptor blockers were approximately twice as likely to have good adherence. Overall, angiotensin-converting enzyme inhibitors appeared to have the second-best level of adherence, followed by calcium channel blockers, although insufficient data were available for definitive rankings. Our findings demonstrate that it is important for clinicians to pay attention to adherence regardless of drug class because adherence was suboptimal for all drug classes and that clinicians should pay special attention to adherence in patients who are prescribed diuretics and β-blockers.
Meta-Analysis: Impact of Drug Class on Adherence to Antihypertensives
Ian M. Kronish, Mark Woodward, Ziad Sergie, Gbenga Ogedegbe, Louise Falzon and Devin M. Mann

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Appendix Table 1. Search terms

Examples given are from MEDLINE (Ovid). Full strategies for other databases are available upon request.

Separate search strategies were devised for each of the drug classes. The structure of each strategy was as follows:

Exp Cardiovascular Diseases/
AND
Drug terms (all terms combined using OR)
AND
Terms for medication compliance (all terms combined using OR)
AND
Terms for study design for MEDLINE, EMBASE and PsycInfo (all terms combined using OR)

Search terms for Angiotensin Converting Enzyme Inhibitors

Search terms for Angiotensin Receptor Blockers

Search terms for Beta Blockers

Search terms for Calcium Channel Blockers

Search terms for Diuretics

Search terms for Alpha Blockers

Search terms for Medication Compliance
exp Patient Compliance/;(complian$ or noncomplian$ or (non adj complian$) or comply or complies or discontinu$ or adher$ or persist$).tw.

Search terms for Study Design
exp Risk Factors/; risk$.tw.; predict$.tw.; determinant$.tw.; associat$.tw.; correlate$.tw.; randomized controlled trial.pt.; exp Randomized Controlled Trials/; controlled clinical trial.pt.; Controlled Clinical Trials/; exp Cohort Studies/; random$.tw.; control$.tw.; cohort$.tw.; prospective$.tw.; observational.tw.; retrospective.tw.; volunteer$.tw.; group$.tw.
Appendix 2. Checklist for determining study quality. Adapted from Peterson et al and Gwadry-Sridhar et al.\textsuperscript{1,2}

- Data sources have been described adequately
- Time frame for the data has been clearly stated
- Inclusion and exclusion criteria are clearly stated
- Duration of the study is appropriate for the objectives of the study
- For studies of adherence after initiating a new drug regimen: examination of the data from a sufficient pre-enrollment period to ensure that the subject was truly naïve to the drug
- For studies measuring compliance: used standard methods for calculating compliance such as mean possession ratio (MPR) or proportion of days covered (PDC), and researchers described how they handled values of adherence > 1; For studies measuring persistence: used standard methods with adequate justification when atypical methods were used
- Appropriate explanation of how researchers handled patients who switched drugs
- Cut-off point for defining compliance or persistence was appropriate and clearly defined (e.g. PDC >80%)
- Controlled for possible variables that may confound the association with adherence
- Disclose potential conflicts of interest

Maximum score of 10 points

References:
항고혈압제의 계열에 따라 투약충실도(adherence)가 차이가 있을까? : 메타분석

신 춘 훈 교수 아주대학교병원 순환기내과

Summary

제정
여러 관찰연구에 따르면 항고혈압제의 계열에 따라 투약충실도가 다르다고 알려져 있다. 본 연구의 목적은 일반적인 임상상황에서 항고혈압제의 계열과 투약충실도 간의 관계를 정량분석하여 항고혈압제의 선택이나 투약충실도를 모니터링하는데 간접적이며 고려할 만한 것이다.

방법 및 결과
이 연구는 2009년 2월 1일까지 영어로 발표된 논문을 대상으로 하였다. 이들 논문 중 항고혈압제의 투약충실도를 측정하거나 투약충실도와 그 변수들에 대한 relative risk(RR)를 계산할 수 있는 충분한 데이터가 포함된 논문을 연구 대상으로 하였다. Inverse-variance-weighted random-effect 모델을 이용한 통계적 기법을 사용하였으며, hazard ratio(HR)와 odds ratio(OR)를 분석하여 계산하였고, HR로 임자 유의성 평가를 하였다. 본 논문의 목적을 충족시키는 데이터를 제공할 수 있는 총 17개 논문을 메타분석하였다.

평균 투약충실도는 베타차단제 28.4%, 이뇨제 51%, 칼슘결핍제 52%, 인자안티에노신-전환효소 억제제(angiotensinconverting enzyme inhibitor, ACEI) 58%, 인자안티에노신-II 수용체 차단제( angiotensin II receptor blockers, ARB) 65%로 ARB 및 ACEI 계열의 약물이 높은 투약충실도를 보였다. 각 약물 계열을 비교할 경우, ARB는 ACEI와 비교하여 HR 1.33(95% CI, 1.13-1.57)으로 더 유의하게 높은 투약충실도를 보였다. 다른 약물과 비교하여도 HR=1.57(95% CI, 1.38-1.79, vs. 칼슘결핍제), HR=1.55(95% CI, 1.73-2.20, vs. 이뇨제), HR=2.09(95% CI, 1.14-3.85 vs. 베타차단제)로 ARB 계열의 약물이 다른 계열의 약물보다 투약충실도에서 의미 있는 비교 우위를 보였다. 역으로 이뇨제는 다른 계열의 약물(ARB, ACEI, 칼슘결핍제, 베타차단제)과 각각 비교하여 의미 있는 열등성을 보였다. 이 결과는 OR를 이용하여 분석해도 동일하였다. 또한, 여러 bias를 보정한 후에도 동일한 결과를 얻을 수 있었다.

결론
일반적인 임상상황에서 항고혈압제의 계열에 따라 의미 있는 투약충실도의 차이가 확실히 있었으며 특히 ARB 및 ACEI가 베타차단제나 이뇨제에 비해 투약충실도가 높았다. 그러나 ARB에서조차도 투약충실도가 65%로 모든 계열의 약물에서 투약충실도는 만족스럽지 않았다.
Commentary

고혈압뿐 아니라 대부분 질환에서 투약처석과가 임상 경과에 영향을 미치는다는 사실은 잘 알려져 있다. 고혈압 처방 중성이 없는 만성질환에서의 투약처석과는 더욱 중요하다. 실제로 고혈압 환자에서 약물치료 후 거의 50% 환자가 1년 이내 약물을 복용하지 않는다고 보고되었다. 1 고혈압 중증도를 높이는 것이 고혈압 치료의 효과를 증진시킬 수 중요하다. 실제 임상에서 약물의 선택은 나이, 성별, 동반질환, 사회 경제적 상태 등을 고려해야 하는데 약물의 종류에 따라서 투약처석과도 차이가 나타나면 이 역시 약물의 선택에 중요한 고려사항이 되어 이 한다.

본 연구에서 투약처석과가 가장 좋은 약물은 ARB로 임상 경과와 어느 정도 일치하는 결과를 보여주었다. 물론 조항처석과에 영향을 미치는 인자로는 약물 부작용, 치료의 유용성과 위험성에 대한 인식, 의사-환자간의 관계, 가격, 의사 접근성 등의 많은 인자들이 있으므로, 본 연구에서 어떤 약물이 효과적으로 투약처석과가 좋고 나쁜 나쁘다고 단정할 수는 없다. 그러나 투약 약물 선택에 고려해야 할 약물의 지속도(persistence)와 순응도(compliance)를 고려하는 것이 중요하다. 지속도는 약물의 복용시점부터 약물이 완전히 복용하지 않게 될 때까지의 일수로 나타나며, 순응도는 약물의 전체 투여 일수로 실제 약물복용 비율로 나타난다. 본 연구에서 약물복용 비율은 주로 지속도를 보여주었으며, 이 역시 결과에 어느 정도는 영향을 주었으리라 생각된다. 이 밖에 본 연구 결과를 논의할 때 고려해야 할 점은 보통의 임상에서 고혈압 환자들은 흔히 2가지 이상의 약물 복용을 요한다. 여러 통계적 방법을 이용하여 보이지 않을 때에도 그 차이가 환자상으로도 영향을 끼치는 문헌들을 선택하였으나 많은 다양한을 설계하였을 가능성이 크다는 점이다. 이런 환자들을 고려하여 본 연구를 해석한다면 실제 임상에서 약물을 선택할 때 많은 도움이 되리라 생각된다. 약 10년 전에 보고되었던 ALLHAT study에서

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