The Association Between Market Availability and Adherence to Antihypertensive Medications: An Observational Study

Charity D. Evans¹, Dean T. Eurich², Xinya Lu¹, Alfred J Remillard¹, Yvonne M. Shevchuk¹ and David Blackburn¹

BACKGROUND
High adherence to angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) reported in observational studies has frequently been attributed to improved tolerability. However, these agents are also relatively new to the market compared to other antihypertensive medications. We aimed to determine if an association exists between adherence and market availability of a specific antihypertensive agent.

METHODS
This retrospective cohort study used administrative data from Saskatchewan, Canada. Subjects were ≥40 years of age and received a new antihypertensive medication between 1994 and 2002. The primary outcome was the proportion of subjects achieving optimal adherence (≥80%) at 1 year, stratified by antihypertensive medication class and the year of availability. Adherence was measured using the cumulative mean gap ratio.

RESULTS
A total of 36,214 subjects met the inclusion criteria. Optimal adherence was observed in 4987 of 8623 (57.8%) subjects receiving ACEIs and 1013 of 1600 (63.3%) subjects receiving ARBs, but adherence appeared inconsistent when examined within each antihypertensive class. A pattern of increasing mean adherence was observed according to availability in the ACEI subgroup (Spearman r = 0.82; P = 0.007) but not the ARB subgroup (Spearman r = 0.41; P = 0.49). However, the association between availability and optimal adherence converged when ARB and ACEI users were combined (Spearman r = 0.85, P < 0.001).

CONCLUSIONS
Optimal adherence with ACEIs and ARBs compared to other antihypertensive agents may be associated with their relative availability. To what extent optimal adherence is also associated with improved tolerability, as currently believed, remains to be determined.

Keywords: adherence; administrative data; angiotensin-converting enzyme inhibitors; angiotensin receptor blockers; antihypertensive agents; blood pressure; hypertension

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METHODS

Data source

The Saskatchewan Ministry of Health maintains several health services databases including prescription drug data, physician services utilization, hospital services utilization, and vital statistics; data collected from these databases contain unique patient identification numbers. All Saskatchewan residents are eligible for provincial health insurance coverage, except inmates of federal penitentiaries and members of the Royal Canadian Mounted Police and Canadian Forces (<1% of the Saskatchewan population), and approximately 90% of the Saskatchewan population is eligible for prescription drug coverage. Residents ineligible for coverage under the drug plan are primarily Registered Indians who have their prescription costs paid for by another government agency. These databases are considered to be of high quality, and have been the source of many observational studies examining medication adherence, including a comparative analysis of adherence to AHT agents.

Study cohort

We designed a retrospective cohort study using a previously defined population of antihypertensive users in Saskatchewan, Canada, between 1 January 1994 and 31 December 2002. In brief, new users of AHT medications, 40 years of age and older, were identified among one of the following prespecified categories: beta-blockers, ACEIs, ARBs, dihydropyridine calcium channel blockers (DHP CCBs), non-DHP CCBs, thiazide diuretics, potassium-sparing diuretics; or one of the following combination products: ACEI + hydrochlorothiazide (HCTZ), ARB + HCTZ, beta-blocker + diuretic, and potassium-sparing diuretic + HCTZ (Supplementary Appendix 1). A new AHT medication user was defined as having no dispensations for any AHT agent in the 5 years prior to the first AHT prescription (index date).

In an attempt to ensure that the AHT was being prescribed for uncomplicated hypertension (i.e., without significant comorbidities that may affect adherence rates), we excluded all subjects who had a history of hospitalization or outpatient physician services in the previous 5 years for any of the following: cardiovascular events (e.g., myocardial infarction, unstable angina, congestive heart failure), diabetes, HIV/AIDS, renal or liver disease, esophageal varices, or solid organ transplant. The observation period began on the first AHT prescription dispensation (i.e., index date) and continued for 1 year (365 days). As medication use during hospital stays is not captured by the Saskatchewan Drug Plan, subjects who were hospitalized for any reason during the observation period were excluded. To ensure reliable estimates of adherence for all patients, only subjects with a full 365 days of follow-up (i.e., still receiving Saskatchewan Health and prescription benefits) were included in the analysis. Finally, we excluded all subjects who filled medications from more than one AHT category during the 1-year follow-up period (i.e., if they switched to a different category of AHT; or had an AHT medication added) to ensure that the AHT cohorts were mutually exclusive. However, switching medications within the same AHT category was allowed.

Endpoints

The primary endpoint was the proportion of subjects achieving optimal adherence (≥80%) at 1 year, stratified by AHT category (Supplementary Appendix 1). Adherence was estimated by subtracting the cumulative mean gap ratio from one. The cumulative mean gap ratio is calculated by dividing the number of days that the AHT medication was unavailable by the number of days in the observation period (365 days). In deriving this measure, it was assumed that the days supply of all dispensations was equal to 34 days, which is the common practice in Saskatchewan. In the case of early dispensations, we applied any estimated remaining medication to future supplies, assuming that all dispensed medications would be consumed in their entirety. The precision of the cumulative gap calculation compared to other commonly used adherence measures has been demonstrated in a previous study among this cohort of AHT users.

Statistical analysis

Baseline characteristics were compared using analysis of variance and chi-square test, as appropriate. For the primary analysis, we calculated the crude and adjusted proportions of individuals achieving ≥80% adherence for each AHT category. Adjusted proportions were estimated from multivariable logistic regression models created with the following covariates considered statistically significant (P < 0.1) or clinically relevant, and included in the models: sex, age at index, Von Korff chronic disease score at index (a well-validated measure of comorbidity derived from medication usage), income security benefits at index (a proxy measure for socioeconomic status), calendar year that the initial AHT was dispensed, and number of physician visits during the observation year, as adherence may be higher in subjects receiving regular follow-up. We also adjusted for concurrent dispensations of the following medications during the observation year: oral diabetes medications and/or insulin, nitrates, statins, Acetylsalicylic Acid (ASA), warfarin, and antidepressants. Additionally, we estimated and adjusted for, the overall prescription burden by totaling the number of selected non-AHT medication classes dispensed (Supplementary Appendix 1) during the observation year. All first order interactions were tested, with none being clinically significant (P < 0.1).

We presented crude and adjusted adherence estimates in order of the year in which each AHT class received their listing on the Saskatchewan formulary, and were therefore available to all Saskatchewan residents. Original formulary dates for diuretics and beta-blockers were not available, as they were first marketed more than 50 years ago. Therefore, dates for these classes were estimated from the literature. Because of significant overlap between availability of different AHT classes, we also examined within-class differences among individuals taking ACEIs and ARBs. In an attempt to characterize trends, for each individual agent we plotted...
the difference in years between its availability compared to the original agent within each class (ACEI: captopril; ARB: losartan) and the proportion of subjects achieving optimal adherence at 1 year. We tested the association using Spearman rank correlation coefficient. We were unable to evaluate within-class difference among other AHT classes as the availability of individual diuretic and beta-blocker agents preceded our data, and all agents within each class of calcium channel blockers (DHP and non-DHP) were available within 12 months of each other.

In secondary analyses, we restricted the cohort to those receiving losartan (ARB), ramipril (ACEI), or amlodipine (DHP CCB) as their initial therapy. Losartan was the first ARB released into the Canadian market (Saskatchewan formulary listing 1996) and was the most frequently prescribed ARB in our cohort. Ramipril and amlodipine were selected as comparators because they shared the closest formulary listings to losartan (amlodipine 1993, ramipril 1995). Thus, all three agents were considered newly available AHT medications, where no generic substitute was available during the study period.

Finally, we compared adherence rates between subjects receiving any ARB medication and those receiving ARB + HCTZ combination products in order to evaluate the influence of a diuretic on the adherence to these medications (Supplementary Appendix 1). In previous observational studies, diuretics have been associated with poor adherence that is frequently attributed to poor tolerability; however, diuretic combination products are typically available after the single AHT agent has already been on the market, and would be considered new medication products.

All analyses were carried out using SPSS version 16.0 for Windows (SPSS, Chicago, IL), and Stata SE, version 10 (StataCorp, College Station, TX). Because all data were de-identified by Saskatchewan Ministry of Health personnel prior to being sent to the investigators, the study protocol was granted a letter of exemption by the University of Saskatchewan Biomedical Research Ethics Board.

RESULTS

We identified 67,939 subjects who were newly initiated on AHT therapy between January 1994 and December 2002 with 52,039 (76.6%) having a minimum follow-up of 365 days without being hospitalized. We further excluded 15,825 (30.4%) subjects who filled more than one category of AHT during the first year of therapy, leaving 36,214 subjects who filled one AHT category exclusively throughout the first year (Figure 1). The mean age was 59.2 (SD 12.8) years and 40% of subjects were male (Table 1). Statistically significant differences were observed among subjects receiving the eligible

![Figure 1. Selection of study participants.](https://academic.oup.com/ajh/article-abstract/26/2/180/216266)
Table 1. Baseline characteristics of study cohort (N=36,214)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>BB</th>
<th>ACEI</th>
<th>ARB</th>
<th>CCB (non-DHP)</th>
<th>CCB (DHP)</th>
<th>Thiazides</th>
<th>BB + Diuretic</th>
<th>ACEI + HCTZ</th>
<th>ARB + HCTZ</th>
<th>K-sparing + HCTZ</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (%)</td>
<td>36.2%</td>
<td>69.0%</td>
<td>86.2%</td>
<td>1600</td>
<td>1170</td>
<td>2111</td>
<td>5690</td>
<td>126</td>
<td>554</td>
<td>453</td>
<td>8980</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Crude adherence ≥80% (%)</td>
<td>14.40%</td>
<td>21.76%</td>
<td>49.87%</td>
<td>1013</td>
<td>385</td>
<td>1111</td>
<td>1922</td>
<td>61</td>
<td>344</td>
<td>305</td>
<td>2101</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean age (years) at index (SD)</td>
<td>59.2 (12.8)</td>
<td>55.9 (11.8)</td>
<td>58.0 (12.1)</td>
<td>60.0 (12.4)</td>
<td>61.9 (12.6)</td>
<td>61.1 (13.5)</td>
<td>58.2 (10.8)</td>
<td>58.4 (10.8)</td>
<td>59.8 (11.9)</td>
<td>59.0 (13.6)</td>
<td>59.0 (13.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean CDS at index (SD)</td>
<td>2.9 (1.8)</td>
<td>2.1 (1.6)</td>
<td>3.9 (1.6)</td>
<td>3.0 (1.7)</td>
<td>3.8 (2.2)</td>
<td>3.0 (1.8)</td>
<td>3.0 (1.6)</td>
<td>3.8 (1.7)</td>
<td>3.8 (1.3)</td>
<td>2.8 (1.4)</td>
<td>2.9 (1.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Index year (%)</td>
<td>1994: 3313 (9.1)</td>
<td>551 (8.0)</td>
<td>746 (8.7)</td>
<td>187 (16.0)</td>
<td>271 (12.8)</td>
<td>400 (7.0)</td>
<td>12 (9.5)</td>
<td>20 (3.6)</td>
<td>0 (0)</td>
<td>1126 (12.5)</td>
<td>&lt;0.0001</td>
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</tr>
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<td></td>
<td>1995: 3583 (9.9)</td>
<td>673 (9.7)</td>
<td>928 (10.8)</td>
<td>199 (17.0)</td>
<td>242 (11.5)</td>
<td>386 (6.8)</td>
<td>17 (13.5)</td>
<td>24 (4.3)</td>
<td>0 (0)</td>
<td>1114 (12.4)</td>
<td>&lt;0.0001</td>
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</tr>
<tr>
<td></td>
<td>1996: 3476 (9.6)</td>
<td>729 (10.6)</td>
<td>842 (9.8)</td>
<td>2 (0.1)</td>
<td>130 (11.1)</td>
<td>168 (8.0)</td>
<td>403 (7.1)</td>
<td>22 (17.5)</td>
<td>31 (5.6)</td>
<td>0 (0)</td>
<td>1149 (12.8)</td>
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<td></td>
<td>1997: 4029 (11.1)</td>
<td>807 (11.7)</td>
<td>1001 (11.6)</td>
<td>50 (3.1)</td>
<td>122 (10.4)</td>
<td>223 (10.6)</td>
<td>524 (9.2)</td>
<td>13 (10.3)</td>
<td>65 (11.7)</td>
<td>8 (1.8)</td>
<td>1216 (13.5)</td>
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<tr>
<td></td>
<td>1998: 3888 (10.7)</td>
<td>863 (12.5)</td>
<td>800 (9.3)</td>
<td>122 (7.6)</td>
<td>127 (10.9)</td>
<td>242 (11.5)</td>
<td>608 (10.7)</td>
<td>11 (8.7)</td>
<td>54 (9.7)</td>
<td>26 (5.7)</td>
<td>1035 (11.5)</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>1999: 4221 (11.7)</td>
<td>888 (12.9)</td>
<td>951 (11.0)</td>
<td>258 (16.1)</td>
<td>113 (9.7)</td>
<td>208 (9.9)</td>
<td>744 (13.1)</td>
<td>13 (10.3)</td>
<td>76 (13.7)</td>
<td>38 (8.4)</td>
<td>932 (10.4)</td>
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<td>2000: 4507 (12.4)</td>
<td>845 (12.2)</td>
<td>1023 (11.9)</td>
<td>328 (20.5)</td>
<td>104 (8.9)</td>
<td>258 (12.2)</td>
<td>849 (14.9)</td>
<td>13 (10.5)</td>
<td>110 (19.9)</td>
<td>64 (14.1)</td>
<td>913 (11.5)</td>
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<td></td>
<td>2001: 4566 (12.6)</td>
<td>776 (11.2)</td>
<td>1103 (12.8)</td>
<td>407 (25.4)</td>
<td>98 (8.4)</td>
<td>279 (13.2)</td>
<td>861 (15.1)</td>
<td>19 (15.1)</td>
<td>95 (17.1)</td>
<td>104 (23.0)</td>
<td>824 (10.2)</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>2002: 4631 (12.8)</td>
<td>775 (11.2)</td>
<td>1229 (14.3)</td>
<td>433 (27.1)</td>
<td>90 (7.7)</td>
<td>220 (10.4)</td>
<td>915 (16.1)</td>
<td>6 (4.8)</td>
<td>79 (14.3)</td>
<td>213 (47.0)</td>
<td>671 (9.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Physician visitsb in observation year (%)</td>
<td>0: 349 (1.0)</td>
<td>66 (1.0)</td>
<td>100 (1.2)</td>
<td>18 (1.1)</td>
<td>10 (0.9)</td>
<td>26 (1.2)</td>
<td>49 (0.1)</td>
<td>0 (0)</td>
<td>7 (1.3)</td>
<td>6 (1.3)</td>
<td>67 (0.7)</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>1–3: 4496 (12.4)</td>
<td>781 (11.3)</td>
<td>1076 (12.5)</td>
<td>180 (11.2)</td>
<td>107 (9.1)</td>
<td>278 (13.2)</td>
<td>745 (13.1)</td>
<td>23 (18.3)</td>
<td>71 (12.8)</td>
<td>52 (11.5)</td>
<td>1183 (12.4)</td>
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<tr>
<td></td>
<td>4–11: 20,423 (56.4)</td>
<td>3617 (52.4)</td>
<td>5092 (59.1)</td>
<td>1010 (63.1)</td>
<td>596 (51.0)</td>
<td>1150 (54.5)</td>
<td>3265 (57.4)</td>
<td>67 (53.2)</td>
<td>357 (64.4)</td>
<td>295 (65.0)</td>
<td>4974 (55.4)</td>
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<tr>
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<td>12+: 10,946 (30.2)</td>
<td>2443 (35.4)</td>
<td>2355 (27.3)</td>
<td>392 (24.5)</td>
<td>457 (39.0)</td>
<td>657 (31.1)</td>
<td>1631 (28.7)</td>
<td>36 (28.6)</td>
<td>119 (21.5)</td>
<td>100 (22.2)</td>
<td>2756 (30.7)</td>
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<tr>
<td>Total concurrent non-AHT medications in observation year (%)</td>
<td>0: 15077 (41.6)</td>
<td>2606 (37.7)</td>
<td>3794 (44.0)</td>
<td>728 (45.5)</td>
<td>321 (27.4)</td>
<td>913 (43.2)</td>
<td>2458 (43.2)</td>
<td>58 (46.0)</td>
<td>278 (50.2)</td>
<td>221 (48.7)</td>
<td>3700 (41.2)</td>
<td>3700 (41.2)</td>
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<td></td>
<td>1–2: 17480 (48.3)</td>
<td>3467 (50.2)</td>
<td>4028 (46.7)</td>
<td>744 (46.5)</td>
<td>625 (53.4)</td>
<td>1005 (47.6)</td>
<td>2719 (47.6)</td>
<td>57 (45.2)</td>
<td>241 (43.5)</td>
<td>200 (44.2)</td>
<td>4394 (48.9)</td>
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<td>3–4: 3244 (9.0)</td>
<td>750 (10.9)</td>
<td>706 (8.2)</td>
<td>111 (6.9)</td>
<td>190 (16.2)</td>
<td>159 (7.5)</td>
<td>452 (7.9)</td>
<td>11 (8.7)</td>
<td>30 (5.4)</td>
<td>31 (6.8)</td>
<td>804(9.0)</td>
<td>804(9.0)</td>
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<td></td>
<td>5+: 413 (1.1)</td>
<td>84 (1.2)</td>
<td>95 (1.1)</td>
<td>17 (1.1)</td>
<td>34 (2.9)</td>
<td>34 (1.6)</td>
<td>61 (1.1)</td>
<td>0 (0)</td>
<td>5 (0.9)</td>
<td>1 (0.2)</td>
<td>82 (0.9)</td>
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(Continued)
### Table 1. (Continued)

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<tr>
<th>Concurrent non-AHT medication in observation year (%)</th>
<th>Overall</th>
<th>BB</th>
<th>ACEI</th>
<th>ARB</th>
<th>CCB (non-DHP)</th>
<th>CCB (DHP)</th>
<th>Thiazides</th>
<th>BB + Diuretic</th>
<th>ACEI + HCTZ</th>
<th>ARB + HCTZ</th>
<th>K-sparing + HCTZ</th>
<th>P value(^a)</th>
</tr>
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<tbody>
<tr>
<td>Diabetes/insulin</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Diabetic/insulin</td>
<td>451 (1.2)</td>
<td>33 (0.5)</td>
<td>246 (2.9)</td>
<td>22 (1.4)</td>
<td>18 (1.5)</td>
<td>15 (0.7)</td>
<td>41 (0.7)</td>
<td>4 (3.2)</td>
<td>11 (2.0)</td>
<td>8 (1.8)</td>
<td>53 (0.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Statins</td>
<td>1232 (3.4)</td>
<td>609 (8.8)</td>
<td>137 (1.6)</td>
<td>10 (0.6)</td>
<td>272 (23.2)</td>
<td>82 (3.9)</td>
<td>42 (0.7)</td>
<td>1 (0.8)</td>
<td>10 (1.8)</td>
<td>3 (0.7)</td>
<td>66 (0.7)</td>
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<td>ASA</td>
<td>648 (1.8)</td>
<td>200 (2.9)</td>
<td>127 (1.5)</td>
<td>13 (0.8)</td>
<td>55 (4.7)</td>
<td>48 (2.3)</td>
<td>74 (1.3)</td>
<td>3 (2.4)</td>
<td>12 (2.2)</td>
<td>5 (1.1)</td>
<td>111 (1.2)</td>
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<tr>
<td>Warfarin</td>
<td>358 (1.0)</td>
<td>89 (1.3)</td>
<td>102 (1.2)</td>
<td>10 (0.6)</td>
<td>34 (2.9)</td>
<td>15 (0.7)</td>
<td>39 (0.7)</td>
<td>0 (0)</td>
<td>4 (0.7)</td>
<td>2 (0.4)</td>
<td>63 (0.7)</td>
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<tr>
<td>Antidepressants</td>
<td>4958 (13.7)</td>
<td>1460 (21.1)</td>
<td>819 (9.5)</td>
<td>162 (10.1)</td>
<td>211 (18.0)</td>
<td>219 (0.4)</td>
<td>745 (13.1)</td>
<td>12 (9.5)</td>
<td>62 (11.2)</td>
<td>43 (9.5)</td>
<td>1225 (13.6)</td>
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<tr>
<td>Income security benefits(^c) (%)</td>
<td></td>
<td></td>
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<tr>
<td>None</td>
<td>28,554 (78.8)</td>
<td>5665 (82.0)</td>
<td>6905 (80.1)</td>
<td>1365 (85.3)</td>
<td>924 (79.0)</td>
<td>1594 (75.5)</td>
<td>4437 (78.0)</td>
<td>94 (74.6)</td>
<td>436 (78.7)</td>
<td>362 (84.3)</td>
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<td>SAP</td>
<td>1045 (2.9)</td>
<td>262 (3.8)</td>
<td>219 (2.5)</td>
<td>22 (1.4)</td>
<td>38 (3.9)</td>
<td>57 (2.7)</td>
<td>123 (2.2)</td>
<td>5 (4.0)</td>
<td>15 (2.7)</td>
<td>4 (0.9)</td>
<td>300 (3.3)</td>
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<tr>
<td>Family-based</td>
<td>400 (1.1)</td>
<td>105 (1.5)</td>
<td>93 (1.1)</td>
<td>25 (1.6)</td>
<td>13 (1.1)</td>
<td>13 (0.6)</td>
<td>59 (1.0)</td>
<td>6 (4.8)</td>
<td>4 (0.7)</td>
<td>6 (1.3)</td>
<td>76 (0.8)</td>
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<tr>
<td>Senior-based</td>
<td>6215 (17.2)</td>
<td>875 (12.7)</td>
<td>1406 (16.3)</td>
<td>188 (11.8)</td>
<td>195 (16.7)</td>
<td>447 (21.2)</td>
<td>1071 (18.8)</td>
<td>21 (16.7)</td>
<td>99 (17.9)</td>
<td>61 (13.5)</td>
<td>1852 (20.6)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Overall test of significance that all 10 treatment groups are similar (analysis of variance and chi-square test).

\(^b\)A single visit includes all services delivered to a single subject by a single physician for the same diagnosis on the same day at the same clinic/location.

\(^c\)None, no income security benefits; SAP, a program of last resort for families and individuals who, for various reasons, including disability, illness, low income, or unemployment, cannot meet basic living costs; family-based, supplements the financial resources of low-income families with dependent children (eligibility based on annual family income and assets); senior-based, supplementary income for subjects ≥65 years who have little or no income other than the federal Old Age Security pension and Guaranteed Income Supplement.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AHT, antihypertensive; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; CDS, chronic disease score (Von Korff)\(^b\); DHP, dihydropyridine; HCTZ, hydrochlorothiazide; K, potassium; SAP, Saskatchewan Assistance Program.
Market Availability and Antihypertensive Adherence

AHT categories; however, few clinically important differences could be identified, except for a lower proportion of men in the thiazide and potassium-sparing + HCTZ groups (Table 1).

Overall adherence comparison between classes

Optimal adherence (≥80%) was observed in 39.8% (14,405/36,214) of all subjects, and a significant difference (P < 0.0001) was observed between the medication categories (Table 1). Optimal adherence was high among users of ARB + HCTZ, ACEI + HCTZ, ARBs, and ACEIs (corresponding adjusted proportions: 0.64, 0.62, 0.61, and 0.57). When these AHT classes were arranged in chronological order of their availability (listing on the Saskatchewan formulary), the frequency of optimal adherence (≥80%) was skewed toward agents available more recently (Figure 2).

Adherence comparison within classes (ACEI and ARB)

For subjects prescribed ACEIs, a pattern of increasing adherence was observed according to availability of each specific agent (Spearman r = 0.82; P = 0.007) (Figures 3a and 4a). An association was not as clear for the ARB class, (Spearman r = 0.41; P = 0.49) (Figures 3b and 4b); however, when the ACEI and ARB subgroups were combined, a similar pattern emerged (Spearman r = 0.85, P < 0.001) (Figure 4c).

Adherence associated with ARBs vs. other AHT categories

Among subjects receiving losartan (ARB), ramipril (ACEI), or amlodipine (CCB), optimal adherence (≥80%) was observed in 59.9% (246/411), 66.7% (1150/1724), and 53.3% (488/915) of subjects, respectively. After multivariable adjustment, the odds of achieving optimal adherence was not significantly different for users of ramipril (adjusted odds ratio (OR) 1.27; 95% confidence interval (CI) 0.99–1.62) or amlodipine (adjusted OR, 0.81; 95% CI, 0.63–1.05) compared to losartan. No significant difference was found between the number of subjects achieving optimal adherence on the combination ARB + HCTZ agents (305/453; 67.3%) compared to those on a single-agent ARB (1013/1600; 63.3%) (adjusted OR, 1.15; 95% CI, 0.92–1.44).

DISCUSSION

We conducted a retrospective cohort study examining adherence among new users of AHT medications. Similar to previous studies, we found clear differences in the rates of optimal adherence according to AHT class, ranging from 67.3% (ARB + HCTZ) to 23.4% (potassium-sparing diuretic + HCTZ). While other investigators attributed these differences to adverse effect profiles, our analyses do not support this theory. The relative “market life” (i.e., length of availability) of AHT agents appears to be a major source of confounding that has not previously been accounted for in AHT adherence research. Indeed, we observed the highest levels of adherence among subjects taking medications most recently available. Importantly, this trend was observed within the ACEI class where adverse effects profiles would likely be similar.29 Therefore, adverse effect profiles do not exclusively explain differences in adherence at the population level for ACEIs; this may potentially hold true for other AHT classes.
as well. To our knowledge, the market availability of medications has never been considered when examining adherence.

Similar to previous studies, the initial comparison of adherence rates between the individual AHT classes appear to suggest that adherence is best with ARBs and poorest with diuretics. However, in analyses restricted to medications available at the same time, neither the ACEI (ramipril) nor DHP CCB (amlodipine) groups differed significantly from the ARB (losartan) group. Furthermore, although diuretics have been associated with poor adherence attributed to troublesome adverse effects, adherence was not appreciably different between subjects receiving ARBs and ARB + HCTZ combination products. In fact, adherence rates were numerically higher among subjects taking the more recently available combination products. Our findings suggest that external factors may be more strongly linked to adherence than the pharmacologic properties of certain AHT medications. For example, newer medications may be perceived as “better” or they may be prescribed for patients who demonstrate a strong motivation to control/treat their hypertension. Indeed, Bourgault et al. found that subjects initiated on ARBs were more likely to start a new course of AHT therapy (any category) if they discontinued their initial ARB compared to those initiated on other AHT agents. ARBs may also be prescribed disproportionately to patients who can afford them. Regardless of the cause, it does appear that patients receiving ARBs are different from those typically receiving other AHT categories. Certainly, more research in this area is warranted, especially now that ARBs are no longer the newest AHT category available.

There are several limitations that must be considered when examining the results. First, we limited the follow-up to 1 year only. However, the first year of therapy is known to
Figure 4. Mean adherence and relative listing date on the Saskatchewan formulary of (a) ACEI compared to captopril, (b) ARB compared to losartan, and (c) ACEI and ARB compared to captopril. (a) Number of years between each ACEI listing on the Saskatchewan formulary and the listing of captopril on the Saskatchewan formulary (first ACEI listed). ▲, Drug (mean adherence (%), SD) listed left to right: captopril (57.9, 43.2); enalapril (71.1, 40.0), lisinopril (74.0, 37.9), quinapril (75.7, 37.2), fosinopril (74.0, 37.7), benazepril (upper) (73.5, 35.9), cilazapril (76.9, 36.0), perindopril (upper) (77.7, 36.7), ramipril (83.5, 37.6). (b) Number of years between each ARB listing on the Saskatchewan formulary and the listing of losartan on the Saskatchewan formulary (first ARB listed). ▲, Drug (mean adherence (%), SD) listed left to right: losartan (79.1, 37.5), irbesartan (78.7, 33.8), valsartan (upper) (83.2, 37.6), candesartan (81.8, 33.8), telmisartan (82.5, 36.1). (c) Number of years between each ACEI/ARB listing on the Saskatchewan formulary and the listing of captopril on the Saskatchewan formulary (first ACEI/ARB listed). ▲, Drug (mean adherence (%), SD) listed left to right: losartan (79.1, 37.5), irbesartan (78.7, 33.8), valsartan (upper) (83.2, 37.6), candesartan (81.8, 33.8), telmisartan (82.5, 36.1). Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
have the lowest adherence rates.\textsuperscript{1,32,33} Second, we restricted our analyses to subjects receiving a single AHT category in order to facilitate clean comparisons. Because of this, we do not know if these patterns are influenced by concurrent AHT therapy, nor do we have data on the 6979 subjects who switched to a different AHT class during the observation period. In addition, we were unable to examine the association between availability and adherence for individual agents in the diuretic, beta-blocker, and calcium channel blocker classes. However, our analytic approach was intentionally similar to previously published reports, and our sample included more than 36,000 subjects. Third, administrative databases inherently lack detailed patient- and prescriber-level information. Therefore, it is possible that not all subjects were prescribed an AHT medication for hypertension. Specifically, certain subjects may have been receiving treatment for conditions that were more acute and periodic, such as transient edema. Also, comparisons of single products vs. their corresponding diuretic-combination products may have introduced indication bias into our comparisons. Nevertheless, we did employ a hypertension definition comparable to similar observational studies using administrative data.\textsuperscript{5,34} and attempted to ensure that the AHT agent had been prescribed solely for uncomplicated hypertension by excluding all subjects who were previously hospitalized for any complicating reason in the previous 5 years. Because the days’ supply was not captured by Saskatchewan Health and Extended Benefits Branch during the period of this study, we had to estimate it. However, the majority of the drugs in the analysis were dispensed on a monthly (34 days) basis, and we have shown this measure to correlate highly with other measures of medication adherence.\textsuperscript{31} Finally, as with all studies employing an ecological design, there is the potential for latent confounding in our analyses.

The longstanding theory that ACEIs and ARBs are associated with higher adherence compared to other AHT exclusively as a result of better tolerability is not supported by our data. Our study suggests that a prescribing bias related to the availability of an agent may also be a factor. Considering that nonadherence to AHT medications has been associated with increases in blood pressure, vascular events, hospitalizations, and healthcare costs,\textsuperscript{34,35} further research is required to better understand this and other underlying factors contributing to medication adherence.

**SUPPLEMENTARY MATERIAL**

Supplementary materials are available at the American Journal of Hypertension online (http://www.oxfordjournals.org/our_journals/ajh/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.
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DISCLOSURE

This study is based in part on de-identified data provided by the Saskatchewan Ministry of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Ministry of Health.

The authors declare no conflict of interest.

REFERENCES

